In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 31, 2022

DEIDRE HENKEL *and* ALEX HENKEL, *parents of* V.H., *a minor*,	*	No. 15-1048V
Petitioners,	*	Special Master Sanders
v.	*	Decision on Entitlement; Influenza ("Flu") Vaccine; FluMist; Narcolepsy; Molecular Mimicry
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Edward M. Kraus, Law Offices of Chicago Kent, Chicago, IL, for Petitioners.
Ryan D. Pyles, United States Department of Justice, Washington, DC, for Respondent.

DECISION ON ENTITLEMENT[1]

On September 21, 2015, Deidre and Alex Henkel ("Petitioners") filed a petition for compensation in the National Vaccine Injury Compensation Program ("the Program").[2] Pet., ECF No. 1. Petitioners alleged that the intranasal seasonal influenza ("flu") vaccine ("FluMist") their minor child, V.H., received on September 24, 2012, caused V.H. to suffer from narcolepsy[3] with cataplexy.[4] *Id.* at 1.

[1] This Decision shall be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet**. In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted Decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755 ("the Vaccine Act" or "Act"). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Narcolepsy is a condition characterized by "recurrent, uncontrollable, brief episodes of sleep, often associated with hypnagogic or hypnopompic hallucinations, cataplexy, and sleep paralysis." *Narcolepsy*, DORLAND'S MEDICAL DICTIONARY ONLINE [hereinafter "DORLAND'S"], https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[4] Cataplexy is "a condition in which there are abrupt attacks of muscular weakness and hypotonia triggered by an emotional stimulus such as mirth, anger, fear, or surprise. It is often associated with narcolepsy." *Cataplexy*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards,[5] I find that Petitioners have failed to provide preponderant evidence that the FluMist vaccine V.H. received on September 24, 2012, was the cause-in-fact of his narcolepsy with cataplexy. Accordingly, Petitioners are not entitled to compensation.

I. Procedural History

Petitioners filed their petition on September 21, 2015. Pet. They filed medical records, Ms. Deidre Henkel's affidavit, and medical literature on September 22, 2015. Pet'r's Exs. 1–10, ECF No. 5; Pet'r's Exs. 11–13, ECF No. 6. Petitioners submitted a statement of completion on October 26, 2015. ECF No. 10.

Respondent filed his Rule 4(c) report on December 24, 2015. Resp't's Report, ECF No. 13. Respondent argued that Petitioners presented insufficient "evidence to establish a causal relationship between [V.H.'s] September 24, 2012 flu vaccination and his narcolepsy with cataplexy[.]" *Id.* at 5. He requested that this case be dismissed. *Id.*

The presiding special master held a status conference with the parties on January 27, 2016. Min. Entry, docketed Jan. 27, 2016; Order, ECF No. 14. Petitioners filed an expert report from Dr. Lawrence Steinman on May 31, 2016. Pet'r's Ex. 14, ECF No. 18-1. Petitioners submitted medical literature and Dr. Steinman's curriculum vitae ("CV") on June 9, 2016. Pet'r's Exs. 15–24, ECF No. 19; Pet'r's Exs. 25–34, ECF No. 20; Pet'r's Exs. 35–42, ECF No. 21.

This case was reassigned to me on January 11, 2017, ECF Nos. 23–27, while the parties engaged in resolution talks. *See* ECF Nos. 28–46. I held a status conference with the parties on June 27, 2018. Min. Entry, docketed June 27, 2018. Respondent stated that he wished to file an expert report. Order at 1, ECF No. 46.

Respondent filed an expert report authored by Dr. Andrew MacGinnitie on July 24, 2018. Resp't's Ex. A, ECF No. 47-1. Respondent submitted medical literature and Dr. MacGinnitie's CV on July 24, 2018, and August 2, 2018. Resp't's Exs. A, Tab 1–Tab 9, ECF No. 47; Resp't's Exs. A, Tab 10–19, ECF No. 48; Resp't's Ex. B, ECF No. 49-1. On August 7, 2018, Respondent filed an expert report and CV from Dr. David Raizen and accompanying medical literature. Resp't's Exs. C–L, ECF No. 50; Resp't's Exs. M–R, ECF No. 51.

I held a status conference in this matter on August 23, 2018. Min. Entry, docketed Aug. 23, 2018; Sched. Order, ECF No. 52. Petitioner filed a supplemental expert report from Dr. Steinman on November 6, 2018, and accompanying medical literature on November 8, 2018. Pet'r's' Ex. 43, ECF No. 54; Pet'r's Exs. 44–53, ECF No. 55. During a December 19, 2018 status

[5] While I have reviewed all of the information filed in this case, only those filings and records that are most relevant to the decision will be discussed. *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision.") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("Finding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered.").

conference, Petitioners indicated that they wished to file an additional report from Dr. Steinman. Order at 1, ECF No. 57; Min. Entry, docketed Dec. 19, 2018. Petitioners submitted said report on February 6, 2019, and medical literature on February 8, 2019. Pet'r's Ex. 54, ECF No. 58; Pet'r's Exs. 55–64, ECF No. 59.

Respondent filed supplemental reports from Drs. MacGinnitie and Raizen, as well as medical literature, on April 22, 2019. Resp't's Ex. S, ECF No. 62-1; Resp't's Ex. S, Tabs 1–9, ECF No. 62; Resp't's Ex. S, Tabs 10–13, ECF No. 63; Resp't's Exs. T–U, ECF No. 64. Petitioners filed an additional report from Dr. Steinman and medical literature on July 16, 2019. Pet'r's Ex. 65, ECF No. 68-1; Pet'r's Exs. 66–69, ECF No. 69. Respondent filed an additional report from Dr. MacGinnitie and medical literature on September 4, 2019. Resp't's Exs. V–W, ECF No. 70. Petitioners filed a status report on September 16, 2019, and stated that they did not intend to file an additional expert report. ECF No. 72 at 1.

An entitlement hearing was originally scheduled for July 20 and July 21, 2020. *See* Hearing Order, ECF No. 73. Petitioners filed medical records and a prehearing brief on April 29, 2020. Pet'r's Exs. 70–75, ECF No. 77; Pet'r's Br., ECF No. 78. Respondent filed his prehearing brief on June 12, 2020. Resp't's Br., ECF No. 80.

On June 17, 2020, Petitioners filed a motion for a status conference to discuss the scheduled entitlement hearing and vacate the briefing schedule in light of the COVID-19 pandemic. ECF No. 81 at 2. I cancelled the July 20–21, 2020 hearing on June 23, 2020. Hearing Order, docketed June 23, 2020. The hearing was rescheduled for March 3 and March 4, 2021, on September 21, 2020. Hearing Order at 1, ECF No. 83. On February 24, 2021, the parties appeared remotely for a test hearing and submitted prehearing submissions. Min. Entry, docketed Feb. 24, 2021; ECF Nos. 85–90.

An entitlement hearing was held remotely in this case on March 3, 2021. Min. Entry, docketed Mar. 3, 2021. Respondent filed a piece of medical literature, which he referenced during the hearing, at my direction on March 4, 2021. Resp't's Ex. X, ECF No. 96-1. On March 31, 2021, Petitioners filed a status report indicating that they did not believe post-hearing briefs were necessary. ECF No. 99.

This matter is now ripe for consideration.

II. Factual Background

A. Medical Records

1. Pre-vaccination Medical Records

V. H. was born on August 3, 2007. Pet'r's Ex. 1 at 78, ECF No. 5-1. His pre-vaccination medical history is notable for childhood illnesses such as ear infections and RSV bronchiolitis.[6]

[6] RSV, or respiratory syncytial virus, "cause[s] respiratory disease that is particularly severe in infants, in whom it causes bronchiolitis[,]" which is "inflammation of the bronchioles[.]" *Respiratory Syncytial*

See, e.g., *id.* at 47, 65. He received his first FluMist vaccination on September 29, 2010, at three years old, without any recorded complications. *See id.* at 83.

On June 29, 2011, V.H. presented to family nurse practitioner Scott Parker at Cedar Valley Medical Clinic. Pet'r's Ex. 4 at 4, ECF No. 5-4. V.H.'s mother reported that he had been "eating a variety of non-food items for the past [six] months." *Id.* Ms. Henkel also noted that V.H. "has been fatigued all the time." *Id.* She reported that V.H. "naps frequently and rests a lot during the day." *Id.* NP Parker assessed V.H. with fatigue and PICA.[7] *Id.* V.H.'s bloodwork was normal. *Id.* at 18.

On August 24, 2011, V.H. presented to Dr. Ellen Arch at Dixie Regional Medical Center for PICA and possible Asperger's Syndrome.[8] Pet'r's Ex. 2 at 10, ECF No. 5-2. Petitioners also discussed V.H.'s unusual behaviors, including "freak[ing] out" if he got dirty and rubbing his siblings' skin. *Id.* at 10–11. Dr. Arch indicated that V.H. may be developing obsessive compulsive disorder ("OCD")[9] or Asperger's Syndrome. *Id.* at 12. Although she favored Asperger's, she did "not feel comfortable making that diagnosis yet." *Id.* Dr. Arch referred V.H. to occupational therapy for assistance with sensory regulation and gave his parents recommendations for managing his behavior. *Id.* at 10, 12.

2. Vaccination and Post-vaccination Medical Records

On September 24, 2012, V.H., then five years old, received the FluMist vaccine intranasally at Color Country Pediatrics. Pet'r's Ex. 1 at 15, ECF No. 5-1. On November 20, 2012, V.H. presented to Cedar Valley Medical Clinic for episodic abdominal pain over the past four days. Pet'r's Ex. 4 at 9. The assessment was abdominal pain, and V.H.'s bloodwork was normal. *Id.* at 10, 23.

On January 30, 2013, V.H. visited physician's assistant ("PA") Taran Hansen at Color Country Pediatrics. Pet'r's Ex. 1 at 12. Ms. Henkel reported that V.H. had "been sleeping more than normal[and] acting generally more fatigued than normal for the past [eight] weeks." *Id.* Ms. Henkel could not "recall an illness that might have triggered the change in behavior[]" and noted that V.H. had not been experiencing fevers. *Id.* Ms. Henkel reported that V.H. was not having consistent abdominal pain or experiencing changes in hair or skin. *Id.* Ms. Henkel noted that V.H. had "not been eating as much as normal, however, [he] has never been one with much of an appetite." *Id.* Ms. Henkel reported no other symptoms. *Id.* V.H.'s physical exam was normal, and

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Virus, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 27, 2022); *Bronchiolitis*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 27, 2022).

[7] PICA refers to "compulsive eating of nonnutritive substances[.]" *PICA*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

[8] Asperger Syndrome is "a pervasive developmental disorder resembling autistic disorder. Being characterized by severe impairment of social interactions and by restricted interests and behaviors, but lacking the delays in development of language, cognitive function, and self-help skills that additionally define autistic disorder." *Asperger Syndrome*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

[9] Obsessive-compulsive disorder is "an anxiety disorder characterized by recurrent obsessions or compulsions that are severe enough to interfere with personal or social functioning." *Obsessive-Compulsive Disorder*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

PA Hansen's assessment was fatigue. *Id.* at 13. PA Hansen ordered bloodwork, which showed no abnormalities. *Id.* at 13–14, 79.

On February 20, 2013, V.H. returned to PA Hansen for a well-child exam. *Id.* at 8. Petitioners reported that "[o]ver the past [one to two] months, [they] have noted [V.H.] being far more sleepy than normal, despite intact, preserved sleep hygiene at nights[and] allowing him at least [ten] hours of sleep per night." *Id.* Petitioners noted that V.H. "has now started falling fast asleep (within minutes) during dinner, sitting upright, etc[.] during the day." *Id.* Petitioners continued that V.H. had a "[history] of sleepwalking and nighttime terrors[,] which have also persisted." *Id.* Petitioners reported that V.H. was "able to still live a good quality life, running and playing as a child his age is expected[]" but that "afterwards, or even if not active any given day, will still quickly fall asleep during conversation, or during other inactive events." *Id.* Petitioners indicated no family history of sleep apnea,[10] narcolepsy, or insomnia. *Id.* They noted that V.H. did not appear to experience trouble breathing during the night and did not snore. *Id.* They reported that V.H. did not exhibit any "odd behavior[,] including jerking, drooling, rapid eye movement, [or] speaking during sleep." *Id.* Petitioners could not identify any changes or triggers that might be impacting V.H.'s behavior. *See id.* V.H.'s physical exam revealed no abnormalities, except for gray and translucent tympanic membranes in his ears. *Id.* at 10. During this visit, V.H. received DTaP, IPV, and MMR vaccinations. *Id.* at 10–11. PA Hansen's assessment was transient excessive sleepiness, and she referred V.H. to Primary Children's Hospital for a sleep study. *Id.*

On February 27, 2013, V.H. returned to Dr. Arch for the first time since 2011. Pet'r's Ex. 2 at 3. Petitioners discussed V.H.'s continuing behavioral and sensory issues, including grabbing other children. *See id.* at 3–4. Dr. Arch noted that "[a] new concern is sleep. [V.H.] is currently sleeping [twelve to fourteen] hours at night along with a [three]-hour nap. He will fall asleep at least once or twice during the day." *Id.* at 4. She continued, "[h]e can fall asleep eating or while playing a game. He is normal upon awakening, but very fussy if one awakens him." *Id.* Petitioners reported that these sleep issues began in "October to November 2012." *Id.* Dr. Arch stated that she "believe[s] that this[11] is anxiety based." *Id.* She opined that V.H. "has features of Asperger['s] [S]yndrome as well. He is likely to be developing OCD." *Id.* Dr. Arch noted that "[t]hese behaviors certainly predated the sleep issues, which began in October to November 2011, [sic] though certainly the sleep issue is not helping." *Id.* Dr. Arch did not want to consider medication until they determined the cause of V.H.'s excessive sleepiness. *Id.*

On March 27, 2013, V.H. presented to Kathleen Pfeffer, M.D., at Utah Sleep & Pulmonary Specialists for a sleep study. Pet'r's Ex. 3 at 15, ECF No. 5-3. Ms. Henkel reported that V.H.'s sleep problems began in mid-November. *Id.* at 9. She noted that V.H. would fall asleep in the car, while watching television, at church, and while playing, sitting, and eating. *Id.* at 13. Dr. Pfeffer stated that "[o]ver the last couple of months[, Petitioners] have noted that [V.H.] is more sleepy during the day, particularly during dinner, sitting upright. He falls asleep during conversations or other interactive events." *Id.* at 15. Dr. Pfeffer noted that "[V.H.] did receive a flue [sic] vaccine at the end of September 2012 with sleepiness beginning over the last several months." *Id.* She

[10] Sleep apnea refers to "transient periods of cessation of breathing during sleep." *Sleep Apnea*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).
[11] It is unclear whether "this" refers to V.H.'s behavioral issues, sleep issues, or both.

stated that she "raise[d] this history given the potential for acquired narcolepsy related to H1N1 vaccine seen more commonly at younger ages." *Id.*

Dr. Pfeffer described V.H.'s sleep study as an "[o]verall . . . beautiful study." *Id.* She concluded that "[V.H.] has at most a very, very mild degree of obstructive sleep apnea[12] and some degree of upper airway resistance associated with [rapid eye movement ("REM")] sleep." *Id.* at 16. Dr. Pfeffer noted that these results did not explain V.H.'s severe daytime sleepiness and stated that she was "worried that he may have narcolepsy." *Id.* Dr. Pfeffer recommended that V.H. undergo a Multiple Sleep Latency Test ("MSLT").[13] *Id.* She stated that she did not think evaluation for an adenotonsillectomy[14] would significantly improve V.H.'s daytime sleepiness because of the mild degree of obstruction observed in the sleep study. *Id.* Dr. Pfeffer also noted that V.H.'s "'sleep' [electroencephalogram ("EEG")] . . . did not reveal any evidence of epileptiform activity[15] . . . ." *Id.*

On March 28, 2013, V.H. followed up with Dr. Pfeffer. *Id.* at 1. Dr. Pfeffer noted that V.H. began "becoming far more sleepy than normal during the day[]" in October or November. *Id.* She noted that V.H. "sleeps anywhere from 8:30 p.m. until 9:00 a.m., and yet takes several naps during the day and constantly falls asleep in inappropriate settings, such as in the midst of a conversation, during dinner, in the bathtub, and always in the car." *Id.* Dr. Pfeffer wrote that "[q]uite concerningly, he did receive a flu vaccine at the end of September and excessive daytime sleepiness began in October/November." *Id.* Dr. Pfeffer also noted that V.H. "has episodes at night where he wakes with bad dreams. These have also increased since October/November." *Id.* She continued that she believed he was experiencing night terrors or confusional arousals but was unsure. *Id.* She noted that V.H. experienced sleep walking episodes involving urinating in inappropriate places. *Id.* Petitioners did not report that they noticed snoring or other respiratory symptoms when V.H. slept, but they noted that "he moves around a lot and kicks and changes body positions." *Id.* They noted, however, that V.H. never complained of pain in his legs. *Id.* Dr. Pfeffer also wrote that "[p]rior to October and November[, V.H.] was described as a very picky eater, but since then he is always hungry." *Id.* Dr. Pfeffer noted that she was addressing

> the relationship between the flu vaccine, his sleepiness, and his increase in appetite in light of concerns that he may have acquired an H1N1 vaccine related insult to

[12] Obstructive sleep apnea "result[s] from the collapse or obstruction of the airway with the inhibition of muscle tone that occurs during REM sleep." *Obstructive Apnea*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022). REM, or rapid eye movement, sleep is "the period of sleep during which the brain waves are fast and of low voltage, and autonomic activities, such as heart rate and respiration, are irregular." *Rapid Eye Movement Sleep*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[13] A multiple sleep latency test, which is used to evaluate "physiologic sleepiness[,]" measures "the speed at which an individual falls asleep when given multiple opportunities to sleep throughout the day and instructed not to resist doing so[.]" *Multiple Sleep Latency Test*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[14] Adenotonsillectomy is "removal of the adenoids and tonsils." *Adenotonsillectomy*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

[15] Epileptiform activity is "interictal activity on an [EEG], characterized by paroxysmal spike, polyspike, or sharp wave discharges[.]" *Epileptiform Activity*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

> his hypothalamus,[16] specifically affecting his satiety center, but more concerningly affecting the sleep/wake center, within which are the orexin[17] secreting cells. These are the cells that are affected in narcolepsy. Vaccine-related narcolepsy is becoming an increasing concern, involving all vaccines, but most commonly [flu].

Id.

Upon physical examination, Dr. Pfeffer stated that V.H. was "a very drowsy appearing young man. He did not actively fall to sleep today, but looked like he was just about to." *Id.* at 1–2. Dr. Pfeffer continued that V.H. appeared "somewhat sedated in his behaviors and had a couple of aggressive outbursts against mom when she should not do what he wanted." *Id.* at 2. Although V.H. appeared sleepy, he did not seem distressed. *Id.* Dr. Pfeffer stated that, based on V.H.'s sleep study, "[V.H.] has the capacity for normal sleep organization and architecture. He did not have a short REM onset, which is typically seen in narcolepsy. He did not have periodic limb movements, which are also frequently seen with narcolepsy." *Id.* Dr. Pfeffer indicated that a narcolepsy diagnosis would depend on the MSLT. *Id.*

On April 13, 2013, V.H. underwent an MSLT following a repeat sleep study. *Id.* at 38. The MSLT indicated a "mean sleep latency [of] 12.4 minutes, mean REM latency [of three] minutes, and there were [four] out of [four] naps with REM sleep." *Id.* at 39. Dr. Pfeffer noted that "[a] normal sleep latency is greater than [ten] minutes, and typically REM sleep does not occur during any naps." *Id.* Dr. Pfeffer stated that V.H.'s "sleep study suggests idiopathic hypersomnia,[18] rather than narcolepsy, although [it] could evolve into narcolepsy." *Id.* Dr. Pfeffer recommended that V.H. take a 1.5-gram dose of Xyrem[19] at bedtime and another dose four hour later. *Id.* at 39, 64. She repeated that she "wonder[s] if this is related to the [flu] vaccine." *Id.* at 39.

On May 8, 2013, Ms. Henkel called Dr. Pfeffer's office to report that V.H. had been wetting the bed when taking Xyrem and had one episode of sleep walking. *Id.* at 62. Petitioner stated that she had not observed an improvement with the medication. *Id.* Dr. Pfeffer increased V.H.'s dose to 2.5 grams twice a night. *Id.* Dr. Pfeffer increased V.H.'s dosage to three grams twice a night on May 16, 2013. *Id.* at 73.

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[16] The hypothalamus is "the ventral part of the diencephalon, forming the floor of the third ventricle[,]" and "[t]he hypothalamic nuclei constitute that part of the corticodiencephalic apparatus that activates, controls, and integrates the peripheral autonomic mechanisms, endocrine activity, and many somatic functions, such as general regulation of water balance, body temperature, sleep, and food intake . . . ." *Hypothalamus*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 7, 2022).

[17] Orexin, also known as hypocretin, refers to "either of two neuropeptides (orexin A and orexin B) produced by the hypothalamus and regulating feeding behavior as well as the sleep-wake cycle." *Orexin*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

[18] Hypersomnia is "excessive sleeping or sleepiness[.]" *Hypersomnia*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[19] Xyrem, or sodium oxybate, is a medication used to treat cataplexy and "excessive daytime sleepiness in patients with narcolepsy." *Xyrem (sodium oxybate) Information*, FDA, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/xyrem-sodium-oxybate-information (last visited Apr. 17, 2022).

On June 13, 2013, V.H, followed up with PA Hansen. Pet'r's Ex. 1 at 5. PA Hansen noted that V.H. had a "recent [history] of cataplexy." *Id.* Petitioners reported "a huge difference in [V.H.'s] demeanor, eyes[,] and overall function levels." *Id.* They indicated that V.H. was tolerating the Xyrem but that he had become "extremely aggressive towards his siblings[]" and easily triggered on his current dosage. *Id.* PA Hansen assessed V.H. with chronic hypersomnia and aggressiveness. *Id.* at 7. PA Hansen prescribed Zoloft[20] to address V.H.'s aggressiveness. *Id.*

On July 15, 2013, Dr. Pfeffer wrote a letter for V.H.'s school explaining his narcolepsy and that naps may help optimize his school performance. Pet'r's Ex. 3 at 78. On July 17, 2013, V.H. followed up with PA Hansen, who noted that V.H.'s Xyrem dosage had recently been reduced to three grams per night. Pet'r's Ex. 1 at 1. Petitioners noted that V.H. appeared to be tolerating Zoloft, but they were unsure whether it was making a difference. *Id.*

On September 18, 2013, V.H. presented to Emmanuel Mignot, M.D. and resident physician Nevin Arora, M.D., at Stanford Sleep Medicine Center for Narcolepsy after being referred by Dr. Pfeffer. Pet'r's Ex. 5 at 3, 7–8, ECF No. 5-5; Pet'r's Ex. 3 at 74. Ms. Henkel reported that V.H.'s symptoms began four to six weeks after V.H. received the FluMist vaccine. Pet'r's Ex. 5 at 3. She reported that V.H. did not nap prior to this. *Id.* Ms. Henkel also reported that V.H. had continuing and progressively scarier night terrors but noted that the Xyrem offered some relief. *Id.* She recalled that V.H. experienced cataplexy symptoms around Easter of that year, when he began collapsing during an Easter egg hunt. *Id.* at 3–4. Ms. Henkel told Dr. Arora that V.H.'s cataplexy symptoms had been worsening since, without improvement with Xyrem. *Id.* at 4. She stated that "[i]t will occasionally present only as eye fluttering, slurred speech, tongue floppiness, dropping of objects, [or his] head dropping back[,] which will sometime [sic] occur when he thinks of something funny[.]" *Id.* Ms. Henkel reported that "[i]t happens often enough [that] his friends and little brother will playfully imitate [V.H's] behavior when it happens." *Id.* Ms. Henkel expressed concern that V.H. may be experiencing sleep paralysis, reporting that "[h]e will endorse being able to hear everything around him but cannot move his body, [which she] associated with [V.H.] waking up or going to sleep but [it] seems to be occurring during sleep." *Id.* Dr. Arora noted that V.H. was experiencing "more restless sleep, associated with lots of movement and going to [the] bathroom. Xyrem has not helped too much with this, and a higher dose causes more aggression . . . ." *Id.* Dr. Arora wrote that "[c]ataplexy and [excessive daytime sleepiness] remains [sic] biggest problems, despite Xyrem and Zoloft." *Id.* Ms. Henkel reported that V.H. "still naps for approximately [three] hours with mild improvement in [excessive daytime sleepiness] when he can wake up on his own." *Id.* Dr. Arora noted that blood testing revealed that V.H. "is HLA[21]

[20] Zoloft, or sertraline hydrochloride, is "a selective serotonin reuptake inhibitor[("SSRI")] used to treat depressive, obsessive-compulsive, and panic disorders[.]" *Zoloft*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[21] HLA refers to human leukocyte antigens, which are "histocompatibility antigens governed by the genes of the HLA complex (the human major histocompatibility complex), a region on the short arm of chromosome 6 containing several genetic loci, each having multiple alleles. Loci are designated by letters; the classical loci are HLA-A, -B, -C, -E, -F, -G, -DP, -DQ, and -DR (there are at least three subloci in the D region)." *HLA*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022); *Human Leukocyte Antigens*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 11, 2022).

positive for DQB1*0602 [("HLA-DQB1*0602"),] the marker associated with narcolepsy." *Id.* On exam, Dr. Arora noted that V.H.'s neck was dropping when he laughed. *Id.* at 6.

Dr. Arora's assessment was "narcolepsy with cataplexy after Flumyst [sic] vaccine." *Id.* at 7. Dr. Arora instructed Petitioners for V.H. to discontinue Zoloft and begin taking Lexapro[22] and directed V.H. to take Xyrem three times per night. *Id.* Dr. Arora also recommended that V.H.'s naps be limited to one hour each. *Id.* Dr. Mignot agreed "with the documented findings and plan of care[.]" *Id.* at 7–8.

On July 9, 2014, V.H. followed up with PA Hansen. Pet'r's Ex. 1 at 91. Petitioners reported that V.H.'s symptoms had improved with medication and that V.H. had been tolerating his medication well. *Id.* The assessments were "[a]ggressiveness[-]improving" and "[c]hronic hypersomnia[-]stable[.]" *Id.* at 93.

On July 21, 2014, V.H. returned to Dr. Pfeffer. Pet'r's Ex. 3 at 75. Dr. Pfeffer stated that V.H. had been diagnosed with narcolepsy and cataplexy, which "may or may not have been related to a flu vaccine." *Id.* Dr. Pfeffer noted that V.H. was taking two grams of Xyrem three times per night. *Id.* Petitioners reported that V.H.'s cataplexy had improved with Lexapro and that he was now having one to two, rather than fifteen, cataplectic episodes per day. *Id.* Although Petitioners reported significant improvement in V.H.'s symptoms, they told Dr. Pfeffer that he was still jerking, twitching, and talking in his sleep. *Id.* Dr. Pfeffer continued V.H.'s Xyrem prescription. *Id.* at 76. She also prescribed Ritalin[23] for additional cataplexy improvement but instructed Petitioners that they would have to experiment with dosing and timing. *Id.* at 75–76.

On August 4, 2014, V.H. presented to Southern Utah Physical Therapy and Rehabilitation for a wheelchair/mobility evaluation. Pet'r's Ex. 6 at 1, ECF No. 5-6. Physical therapist Tyler Brinkerhoff noted that V.H. was asleep during the evaluation and that Ms. Henkel had to carry him to and from the car. *Id.* The physical therapist determined that V.H. needed a mobility device and recommended a Convaid Stroller. *Id.*

On October 22, 2014, V.H. presented to Jamie Cox, APRN at Cedar Valley Medical Clinic. Pet'r's Ex. 74 at 5, ECF No. 77-5. APRN Cox wrote that V.H. "presents with his mother who states that he was recently diagnosed with [n]arcolepsy about a year and a half ago and his sister was diagnosed this month. Their father is now experiencing similar symptoms and tested negative for the genetic mutation." *Id.* Ms. Henkel told APRN Cox that the family had moved into the basement of an older house "[two] years ago and that is about the time symptoms started." *Id.* Ms. Henkel indicated that they had not had their water or soil tested. *Id.* She noted that V.H. previously "would eat the paint off the walls[]" due to his PICA. *Id.* APRN Cox suspected that V.H. had been

[22] Lexapro, or escitalopram oxalate, is "a[n SSRI] . . . used as an antidepressant[.]" *Lexapro*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022); *Escitalopram Oxalate*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[23] Ritalin, or methylphenidate hydrochloride, is "a central stimulant used in the treatment of attention-deficient/hyperactivity disorder, narcolepsy, and certain forms of depression . . . ." *Ritalin*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022); *Methylphenidate Hydrochloride*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

exposed to lead and ordered bloodwork testing V.H.'s lead levels, iron and iron binding capacity, and ferritin. *Id.* at 7–8. V.H.'s bloodwork was normal. *Id.* at 8.

On November 5, 2014, V.H. returned to Stanford, presenting to Dr. Mignot and resident physician Jaynesh Patel, M.D. Pet'r's Ex. 5 at 12. Petitioners reported dramatic improvement in V.H.'s sleep quality since their last visit and that V.H.'s enuresis[24] had completely resolved. *Id.* Petitioners stated that V.H. was more active and generally able to participate in school. *Id.* However, they noted that V.H. was still experiencing multiple, though mostly minor, cataplexy episodes throughout the day. *Id.* They also reported that V.H. had started Ritalin. *Id.* Drs. Patel and Mignot increased V.H.'s Xyrem to 2.25 grams three times per night and added Effexor.[25] *Id.* at 15–16.

V.H. followed up with PA Hansen on January 13, 2016, for a well-child exam. Pet'r's Ex. 71 at 5, ECF No. 77-2. V.H. was "thriving and doing well in school[]" on his medication regimen but was noted to be "sleeping at times[]" on exam. *Id.* at 7–8. Also on January 13, 2016, V.H. presented to Robert Pearson, M.D. at Canyon View Ear, Nose, & Throat. Pet'r's Ex. 70 at 1, ECF No. 77-1. Dr. Pearson refilled V.H.'s Xyrem. *Id.* at 2.

On February 15, 2017, V.H. returned to Dr. Pearson and was doing well. Pet'r's Ex. 73 at 12, 14, ECF No. 77-4. Dr. Pearson noted that V.H. "is benefitting from Xyrem usage with [an] improved Epworth[26] score and near elimination of cataplexy." *Id.* at 14. On August 1, 2017, V.H. followed up with Dr. Pearson to "get a new [prescription]." *Id.* at 9. For a month, V.H. had been on a new medication regimen, taking 4.5 grams of Xyrem twice per night and switching to Prozac[27] from Lexapro. *Id.* Dr. Pearson noted that V.H. was "much improved[]" on this regimen. *Id.*

On April 26, 2019, V.H. returned to PA Hansen. Pet'r's Ex. 72 at 15, ECF No. 77-3. Ms. Henkel reported that V.H. had been needing to take Ritalin twice per day for the last several months because of activities he was participating in. *Id.* Ms. Henkel told PA Hansen that V.H. was "sleepy all the time[]" if not taking Ritalin. *Id.* PA Hansen increased V.H.'s Ritalin dosage. *See id.* at 17. V.H. later returned to taking Xyrem three times per night. *See* Pet'r's Ex. 73 at 2.

B. Petitioner's Affidavit and Fact Testimony

Petitioners filed an affidavit from Ms. Henkel on September 22, 2015. Pet'r's Ex. 8, ECF No. 5-8. Ms. Henkel stated that she and her husband noticed that V.H. "seemed to be tired more

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[24] Enuresis is urinary incontinence. *Enuresis*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

[25] Effexor, or venlafaxine hydrochloride, is used as an antidepressant and antianxiety agent. *Effexor*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 7, 2022); *Venlafaxine Hydrochloride*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 7, 2022).

[26] The Epworth Sleepiness Scale "measur[es] how sleepy a person is during daytime or working hours, using a scale of 1 to 5 for whether the person is unlikely to likely to fall asleep in a serious of situations such as watching television, having a quiet conversation, or being stalled in traffic." *Epworth Sleepiness Scale*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

[27] Prozac, or fluoxetine, is an SSRI. *Prozac*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022); *Fluoxetine*, DORLAND'S, https://www.dorlandsonline.com (last visited Mar. 17, 2022).

frequently than usual[]" in "late October[]" of 2012. *See id.* ¶¶ 3–4. She continued that "in mid to late November, [they] noticed V.H. was falling asleep frequently during the day." *Id.* ¶ 5. Ms. Henkel stated that V.H. "was falling asleep at least once a day for a few hours at a time[]" by January of 2013. *Id.* ¶ 6. Ms. Henkel also recounted some of V.H.'s medical treatment. *See id.* ¶¶ 7–14.

Both petitioners appeared at the entitlement hearing, and Ms. Henkel testified. She described V.H.'s sleep schedule prior to the age of five as "very good[.]" Tr. 15:3–5. She recalled that V.H. began sleeping through the night at eight months old. Tr. 15:6–7. Ms. Henkel stated that V.H. "slept soundly[and] never had anything that way to wake him up, and he continued to do that quite a ways through." Tr. 15:10–12. She recalled that V.H. was taking two naps per day when he was in day care at two years old and that they used the same schedule at home. Tr. 15:13–16. Ms. Henkel stated that the day care switched to one nap per day and that this continued as V.H.'s nap schedule until V.H. left day care in May of 2011. Tr. 15:18–21. She explained that V.H. "still would trickle and have naps occasionally, it just wasn't as strictly enforced." Tr. 15:21– 23. She stated that V.H. "completely stopped napping the summer of 2011[,]" when he was three and a half to four years old. Tr. 15:23–16:2. Ms. Henkel also recalled that V.H. had no sleep problems, such as nightmares or night terrors, before he was five years old. Tr. 16:3–7. Asked to clarify her later statement to Dr. Mignot that V.H. "would never nap before" his 2012 FluMist vaccine, Ms. Henkel explained that she was referring to the time period "when V.H. stopped napping, so the summer of 2011 until October of 2012." Tr. 31:4–15.

Ms. Henkel was asked about V.H.'s visit with NP Parker in June of 2011, specifically the note indicating that V.H. was experiencing fatigue and frequently napping or resting. Tr. 16:8–17. Ms. Henkel stated that Petitioners took V.H. in because of concern about V.H.'s sucking on nonfood items. Tr. 16:18–21. She continued that NP Parker asked whether V.H. was tired more. Tr. 16:21–22. Ms. Henkel explained that "[V.H.] sleeping or being a little bit more tired than" usual "must have been something [they] were a little bit concerned about[.]" Tr. 16:22–24. Ms. Henkel noted, however, that "[she] do[es] not believe there was any reason that [they] thought there was anything more than taking the kids in when they were sick and being just a little bit extra tried. It was just one of the symptoms at that point." Tr. 16:24–17:3. Ms. Henkel further indicated that this occurred around the time that V.H. was switching from having one nap per day to having no naps, stating that "[V.H.] stopped napping shortly after that visit that summer, so he would have been transitioning from that, and he was also getting off of that preschool schedule[.]" Tr. 17:6–9. Ms. Henkel stated that Petitioners did not address V.H.'s sleep with NP Parker after this visit because "there was no extra concern[,]" as V.H. had "stopped napping completely after that point[.]" Tr. 17:10–14. Ms. Henkel indicated that they never had any other concerns about V.H.'s sleep prior to his receipt of the FluMist vaccine in 2012. Tr. 17:15–19.

Ms. Henkel recalled that after V.H. received his September 2012 FluMist vaccination, around mid-October of 2012 and the end of October, Petitioners "started noticing that he was sleeping through the daytime more than just a typical nap." Tr. 18:23–19:3. Ms. Henkel stated that they thought at first that V.H. might be going through a growth spurt that would pass. Tr. 19:5–8. She explained that she knew they started noticing that V.H. was having sleep problems in October of 2012 because she had a baby in late September and was awake with her during the night and using a nap schedule. Tr. 19:9–14. Ms. Henkel continued that "things progressed and got worse

through November[]" and that "either the baby or V.H.[] . . . were always sleeping." Tr. 19:16–18. Ms. Henkel also recalled a time when her husband was out of town for two weeks and when she was struggling to manage her baby and V.H.'s inability to sleep though the night and tendency to sleep at times during the day. *See* Tr. 19:19–20:18.

Ms. Henkel was asked about V.H.'s medical visit for abdominal pain in November of 2012. Tr. 20:19–20. She explained that "[t]his was the point V.H. was coming in [Petitioners' room during] the night . . . . This was not a normal behavior [for] him." Tr. 20:21–24. Ms. Henkel continued that, although there were no outward signs that V.H. was ill, she took him for medical treatment "after multiple nights of him coming in every night and saying that he had a stomachache, . . . and it was getting him out of bed multiple times a night." Tr. 20:24–21:6. She noted that V.H. only complained about his stomachache at night. Tr. 21:6–8. Ms. Henkel explained that she did not address V.H.'s sleep problems during this visit because he was "breaking his sleep schedule at night, so of course he[is] getting more sleep in in [sic] the daytime. And just, again, thinking maybe [it was] a growth spurt or something to that matter." Tr. 21:12–20. Ms. Henkel continued that her concern was the stomachache because "[t]hat[is] what he would be complaining about in the night[,] and [she] did[not] really have anything else to go off of." Tr. 21:20–23. She stated that V.H. stopped complaining about a stomachache about two days after that medical appointment. Tr. 22:1–3.

Ms. Henkel stated that Petitioners sought a medical evaluation for the changes in V.H.'s sleep patterns in January of 2013 because "[h]is smaller naps had turned into a three-hour nap on the couch[] . . . ." Tr. 22:4–10. She recalled that when she would wake V.H. up, he would claim he had not been asleep. Tr. 22:10–13. Ms. Henkel continued that "[t]he amount of sleep that was happening was getting worse and worse as it was going. And his nighttime was very disrupted still. He never got back off that disruption of nighttime sleep. And he was scared to sleep in his own bed at that point." Tr. 22:15–19. During cross-examination, Ms. Henkel was asked to explain why she would have reported on January 30, 2013, that she had noticed V.H.'s symptoms for the past eight weeks. Tr. 45:3–7. She answered, "[b]ecause that was a significant change that carried on more than a couple days. It was . . . a longer period of time. And had[not] stopped." Tr. 45:13–16. Respondent's counsel noted that eight weeks before January 30, 2013, would have been December 5, 2012, and he asked Ms. Henkel to explain why "eight weeks might have stuck in [her] mind as a date of reporting symptoms[.]" Tr. 45:17–20. She responded that "the symptoms would have been starting—[she] think[s] that was [her] timeline, was knowing like November was really bad. [She] do[es not] know how, if it was just the way it got grouped together, but [she] know[s] that[] . . . December was really bad." Tr. 46:4–8.

Ms. Henkel stated that Petitioners took V.H. back to PA Hansen in February of 2013 because V.H.'s problems were continuing to worsen. Tr. 23:17–21. Ms. Henkel stated that "[t]he nighttimes [sic] were very, very disturbed. [V.H.] was saying[] . . . that he was having dreams or that there was [sic] things in his room that he could see. He started falling asleep in the bathtub . . . Sitting up straight, [they] would catch[] him like sleeping, nodding sideways and sleeping sitting up." Tr. 23:22–24:3. She continued that V.H.'s eyes had changed. Tr. 24:5. She stated that V.H.'s eyes "used to be bright and sparkly and wide open and they went [] dark [with] rings underneath them[,] and he could[not] hold his eyes open more than halfway." Tr. 24:5–8. On cross, Respondent's counsel asked Ms. Henkel about her statement to PA Hansen in February of 2013

that V.H. had been experiencing symptoms for the past one to two months. Tr. 46:9–15. She explained that she "think[s] the time period . . . probably just seemed a lot closer to [her] than it was. [She] know[s] that [she] can relate back to that just because of [her husband's] work visit and knowing that those sleeps were disrupted from then. [They] have pictures from November and December." Tr. 46:16–20.

I also asked Ms. Henkel to clarify whether the timeline of V.H.'s symptoms was reported correctly to V.H.'s pediatrician. Tr. 47:11–14. Ms. Henkel stated that she did not believe the timing was incorrectly noted. Tr. 47:15. She explained that she "[t]hinks the more significant, like the worst things got was later in that time period. And so it was very significant, hugely noticeable by December. Like there was no getting around that. By December, it was really rough." Tr. 47:15–19. Ms. Henkel continued that she "do[es not] know if [she] just kind of had grouped it together going like, we thought it was a growth spurt before, but this is[] . . . from this point forward, this is not. And [she] think[s her] timeline maybe just felt like it had been a shorter period of time." Tr. 47:20–24. I asked Ms. Henkel if V.H.'s symptoms progressively worsened rather than appeared suddenly. Tr. 47:25–48:2, 48:6. She explained that V.H.'s sleep problems and fatigue progressively worsened, stating "[t]he sleeping just going from one nap to two naps to three naps to a longer period of time, too, and it just progressed on top of each other[.]" Tr. 48:3–7.

Ms. Henkel stated that PA Hansen indicated in February of 2013 that she suspected that V.H. was suffering from sleep apnea and referred them to Dr. Pfeffer. Tr. 24:19–23. Ms. Henkel recalled that PA Hansen did not suspect that V.H. was suffering from narcolepsy but that Dr. Pfeffer suspected narcolepsy after V.H.'s first sleep study. Tr. 24:16–19, 25:17–21. Ms. Henkel stated that Dr. Pfeffer "very strongly thought" that V.H.'s possible narcolepsy was due to the FluMist vaccine. Tr. 25:25–26:8.

Ms. Henkel recalled speaking with Dr. Pfeffer on the phone after V.H. underwent his MSLT. Tr. 26:21–25. Ms. Henkel stated that Dr. Pfeffer "told [her] that [V.H.] was positive for narcolepsy and . . . started laying out some treatment options." Tr. 26:25–27:2. Ms. Henkel stated that she told Dr. Pfeffer that V.H. had started experiencing cataplexies. Tr. 26:4–6. Ms. Henkel explained that she learned what cataplexies were during their first appointment with Dr. Pfeffer but that V.H. had not experienced one yet. Tr. 26:13–21. Ms. Henkel stated that they first observed V.H. having a cataplexy when he went to pick up an Easter egg but "just crumbled to the ground[.]" Tr. 27:22–28:1. She continued that V.H. began having multiple cataplexies per day from that point on. Tr. 28:2–3. Ms. Henkel stated that Dr. Pfeffer started V.H. on Xyrem, which helped but also caused behavioral side effects. *See* Tr. 28:4–29:5. Although V.H. was prescribed Zoloft to help with his behavioral changes, Ms. Henkel stated that they "did[not] see a huge improvement with that." Tr. 29:8–13.

Ms. Henkel discussed V.H.'s first appointment with Dr. Mignot. *See* Tr. 29:17–33:7. She recalled V.H. had a cataplexy in Dr. Mignot's office and that Dr. Mignot diagnosed V.H. with narcolepsy with cataplexy. Tr. 32:1–5. Petitioner stated that they discussed the FluMist vaccine with Dr. Mignot "extensively" because V.H. received it close to onset. Tr. 32:9–11. Ms. Henkel recalled that Dr. Mignot was "running a study also at that point, from the FluMist and that, and he talked with his students or the colleagues that had come in briefly about that." Tr. 32:12–14. Ms. Henkel stated that they also discussed V.H.'s genetics. Tr. 32:15–18. She noted that Dr. Mignot

adjusted V.H.'s medication and that the medication changes were helpful. Tr. 32:21–33:15. She recalled returning to Dr. Mignot about one year later for another medication adjustment when V.H. began experiencing worsening symptoms following a growth spurt. Tr. 34:9–25.

Ms. Henkel discussed V.H.'s medication regimen as of the hearing date in 2021. Tr. 35:5–12. She stated that V.H. was taking Xyrem three times per night, Prozac, and Concerta,[28] as well as Ritalin as needed. *Id.* Ms. Henkel indicated that Petitioners had never received an explanation for V.H.'s narcolepsy besides the FluMist vaccine and V.H.'s genetic makeup. Tr. 35:13–19. Ms. Henkel stated that no one else in their family had been diagnosed with narcolepsy but indicated that other family members had been evaluated for sleep problems. Tr. 35:20–36:12. She explained that her oldest daughter was evaluated "as soon as [providers] found out that V.H. had narcolepsy, they just wanted to make sure it was[not] something [she was] dealing with, even though none of those symptoms were what she was having, hers were more anxiety[.]" Tr. 36:4–8. Ms. Henkel stated that her husband has sleep apnea. Tr. 36:8–9.

Discussing V.H.'s current condition, Ms. Henkel stated that V.H. was doing well and was very healthy besides his narcolepsy. Tr. 36:14–20. She indicated that Petitioners had "made lots of adjustments and accommodations to make his life easier[] . . . ." Tr. 36:15–16. Ms. Henkel discussed the changes their family had made, the impact of V.H.'s narcolepsy on his activities, and her concern for V.H.'s future. *See* Tr. 36:23–43:24.

III. Experts

A. Expert Review

1. Petitioners' Expert, Lawrence Steinman, M.D.

Dr. Steinman received his medical degree from Harvard University in 1973. Pet'r's Ex. 76 at 1, ECF No. 86-7. He completed his internship and two residencies at Stanford University Hospital in surgery, pediatrics, and pediatric and adult neurology, respectively, and had various fellowships, between 1973 and 1980. *Id.* He became an assistant professor at Stanford University in 1980 and has been a full professor in Stanford's departments of neurology and neurological sciences, pediatrics, and genetics since 1991. *Id.* Dr. Steinman was the chairman of Stanford University's immunology program from 2002 to 2011 and has been the incumbent of the GA Zimmerman Chair as professor of neurological sciences, neurology, and pediatrics since 2008. *Id.* Dr. Steinman achieved board certification by the American Board of Psychiatry and Neurology in 1984. *Id.* at 2. He has won multiple awards and is a member of numerous professional organizations pertaining to neurology and immunology. *Id.* Dr. Steinman has acquired more than forty patents and held numerous administrative, advisory, editorial, and business posts over the course of his career. *Id.* at 2–4; Pet'r's Ex. 14 at 2–3, ECF No. 18-1. Dr. Steinman's posts include "serv[ing] on expert panels for the Institute of Medicine of the National Academy of Sciences on matters pertaining to vaccination . . . ." Pet'r's Ex. 14 at 2. Additionally, he is an "elected member

[28] Concerta, or methylphenidate hydrochloride, is "a central stimulant used" to treat various conditions, including narcolepsy. *Concerta*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022); *Methylphenidate Hydrochloride*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 17, 2022).

of both the National Academy of Medicine and the National Academy of Sciences." *Id.* at 3. Dr. Steinman stated that he "was the first and perhaps the only immunologist elected to the National Academy of Science." Tr. 51:22–23. He has testified in the Program numerous times. *See* Pet'r's Ex. 14 at 3. He has recently testified for petitioners on many occasions but served as an expert witness for the U.S. Department of Justice in vaccine cases during the 1980s and has worked with the Department of Justice in other matters. *Id.*

Dr. Steinman is listed as an author on 597 publications, as of January 2021. Pet'r's Ex. 76 at 5–48. His work "includes several papers on molecular mimicry, several papers on narcolepsy, and one world-wide patent application on narcolepsy and [flu] vaccines." Pet'r's Ex. 14 at 3–5. Dr. Steinman published his first paper on narcolepsy, which identified a genetic marker related to narcolepsy, in 1988. Pet'r's Ex. 14 at 4.

Dr. Steinman explained that his "primary branch is immunology[and] secondary branch is cellular or neurobiology." Tr. 51:23–25. Dr. Steinman has experience treating pediatric and adult neurology patients. Pet'r's Ex. 14 at 2. He explained that he primarily sees patients for "multiple sclerosis related diseases, neuromyelitis optica, myasthenia gravis, and so on." Tr. 53:14–17. Although he has treated patients for narcolepsy in the past, Dr. Steinman stated that Dr. Mignot now handles narcolepsy cases at Stanford. Tr. 119:2–5. During the hearing, Dr. Steinman was admitted as an expert in neurology and immunology. Tr. 61:2–6.

2. Respondent's Expert, Andrew J. MacGinnitie, M.D., Ph. D.

Dr. MacGinnitie received his Ph.D. in pathology from the University of Chicago in 1996 and his medical degree from the same institution in 1998. Resp't's Ex. B at 1, ECF No. 49-1. He completed a residency in pediatrics through the Boston Combined Residency Program from 1998 to 2001 and a fellowship in allergy/immunology at Children's Hospital – Boston from 2001 to 2004. *Id.* He was also a clinical fellow in pediatrics at Harvard Medical School from 1998 to 2004. *Id.* Dr. MacGinnitie was an assistant professor in pediatrics at University of Pittsburgh between 2004 and 2011. *Id.* In 2011, he joined the faculty of Harvard Medical School, where he has remained since. *See id.* Dr. MacGinnitie has served as an attending physician in pediatrics and allergy/immunology at children's hospitals in Pittsburgh and Boston throughout his respective academic appointments. *Id.* at 1–2. He has been the clinical director of the division of immunology at Children's Hospital – Boston since 2015. *Id.* at Dr. MacGinnitie has held multiple other positions during his career. *Id.* at 2–3. He belongs to the Clinical Immunology Society and the American Academy of Allergy, Asthma, and Immunology. *Id.* at 3. He has also participated in grant review and editorial activities. *Id.* at 3–4. Dr. MacGinnitie is board certified in allergy/immunology as well as pediatrics and sees over 1,600 patients per year. Resp't's Ex. A at 2, ECF No. 47-1. He is listed as an author on more than thirty-five publications. *See* Resp't's Ex. B at 11–15. He has "perform[ed] research and [] published articles in a number of areas related to [a]llergy/[i]mmunology, including food allergy, vaccine reactions, and primary immunodeficiency." Resp't's Ex. A at 2. He has previously served as an expert in the Program. *Id.* Dr. MacGinnitie was admitted as an expert in pediatric immunology during the hearing. Tr. 196:10–13.

3. Respondent's Expert, David M. Raizen, M.D., Ph. D.

Dr. Raizen received his medical degree and Ph.D. from University of Texas Southwestern Medical School in 1997. Resp't's Ex. D at 1, ECF No. 50-2. He completed an internship in internal medicine, a residency in neurology, and a postdoctoral research fellowship in sleep medicine all at the University of Pennsylvania between 1998 and 2004. *Id.* He has been on the faculty of University of Pennsylvania's medical school since 2007 and has been an associate professor of neurology since 2016. *Id.* He also holds a secondary appointment in the departments of medicine and genetics. *Id.* Dr. Raizen has been certified by the American Board of Psychiatry and Neurology since 2003 and was certified by the now-defunct American Board of Sleep Medicine in 2005. *Id.*; Tr. 164:16–19. He is a member of multiple professional societies pertaining to neurology and sleep medicine and has participated in grant review, consulting, peer review, and other activities. Resp't's Ex. D at 1–3; Resp't's Ex. C at 2, ECF No. 50-1. He is listed as an author on over forty publications and serves as the director of "a research group aimed at understanding fundamental mechanisms regarding sleep and wake." Resp't's Ex. D at 3–5; Resp't's Ex. C at 2. Dr. Raizen has more than fourteen years of experience treating patients with sleep disorders. Resp't's Ex. C at 1. He stated that he frequently considers narcolepsy diagnoses for his patients, which involves interpreting the results of sleep testing and sometimes blood testing, including HLA types. *Id.* Dr. Raizen has stated that he has "followed the medical literature on the pathogenesis of narcolepsy closely[]" because many of his patients ask him about it. *Id.* Dr. Raizen testified that, in additional to his clinical responsibilities and teaching, he spends significant time "doing research into fundamental mechanisms of sleep and . . . fatigue[]" with a "laboratory-based approach[.]" Tr. 164:23–165:11. During the hearing, Dr. Raizen was admitted as an expert in "neurology with a special emphasis in sleep medicine." Tr. 166:22–167:5.

B. Expert Reports and Testimony

1. Petitioners' Expert, Dr. Steinman

Dr. Steinman submitted four expert reports in this case and testified at the hearing. Pet'r's Ex. 14; Pet'r's Ex. 43, ECF No. 54-1; Pet'r's Ex. 54, ECF No. 91-1[29]; Pet'r's Ex. 65, ECF No. 68-1; *see* Tr. 50–161, 259–61. During his testimony, Dr. Steinman described narcolepsy as a "not [] uncommon disease[]" in which "transmission in a very select group of neurons in [the] brain is impacted and leads to [] devastating clinical manifestations . . . ." Tr. 61:11–15. He continued that both a person's genetics and environment contribute to the development of the disease. Tr. 61:18–22. Dr. Steinman explained that narcolepsy and cataplexy are "often related[]" because "somehow the innervation from the neurons that secrete what is called hypocretin and is synonymous with orexin[30] . . . lead to this abrupt motor disturbance called cataplexy where you can get overexcited . . . and then [] lose your postural tone and [] collapse to the floor." Tr. 61:25–62:9. Dr. Steinman explained that, like in dogs, the genetic component of narcolepsy is "a mutation in the hypocretin receptor type 2. In humans, the association is with one of the genes of our histocompatibility complex, a gene called HLA-DQ, and a particular [HLA-DQB1*0602]." Tr. 62:10–15. Dr. Steinman stated that "[n]early all diseases that we think are autoimmune are related to HLA." Tr. 62:15–16. He noted, however, that "[i]n narcolepsy, you have the strongest relationship between

[29] Petitioners refiled Dr. Steinman's third expert report, Exhibit 54, to correct citations on March 1, 2021. All further citations to Petitioner's Exhibit 54 will refer to ECF No. 91-1.

[30] "Hypocretin" and "orexin" will hereafter be used interchangeably.

HLA and any of the diseases that we think are immune, [sic] and that association is [ninety-nine] percent." Tr. 62:19–21. Dr. Steinman averred that "nearly everyone with narcolepsy" has this gene. Tr. 62:22–25. Dr. Steinman explained, however that although "everyone with narcolepsy has that particular gene[,] most people who have that gene do not have narcolepsy. . . . [I]t is not sufficient, something else has to hit a human besides [having HLA-DQB1*0602]." Tr. 63:2–8.

When asked to elaborate on the pathogenesis of narcolepsy, Dr. Steinman stated that "the system in the brain that[is] involved in sleep and cataplexy is somehow impacted, and impacted [such that] that it [is] wrecked, destroyed, [and] immunologically attacked . . . ." Tr. 77:12–15. He continued that a narcoleptic colony of dogs housed at Stanford "represent another way. There would be a genetic mutation in the receptor, and that[is] known to be the cause in the dogs." Tr. 77:15–18. Dr. Steinman explained that the pathogenesis of narcolepsy involves "something [being] attacked in that very restricted pathway in the brain." Tr. 77:18–19. Dr. Steinman explained that this pathway in the brain "[is] the hypocretin neurons[,] . . . [m]eaning the neurons contain hypocretin, and the hypocretin is a transmitter that interacts with a receptor, or the hypocretin receptor." Tr. 77:20–78:2. When asked to explain what animal models contribute to our understanding of the causes of narcolepsy in humans, Dr. Steinman stated that "the animal model is a high-fidelity version of the human disease, the only major difference is very significant. In the dogs, there[is] a mutation in the hypocretin receptor[.]" Tr. Tr. 78:3–10. However, "in humans, there is not, and the disorder must be due to something else, and the Latorre paper[31] said that something else is pretty clearly an immune response to orexin or hypocretin itself." Tr. 78:10–13 (citing Pet'r's Ex. 49, ECF No. 55-6).

When I questioned Dr. Steinman later, I asked him to compare the genetic component of narcolepsy in dogs to the genetic component in humans. Tr. 139–140. Dr. Steinman explained that "[a] mutation in the hypocretin receptor gene" causes narcolepsy in dogs and might in humans as well. Tr. 140:7–10. However, he clarified that he believes narcolepsy in humans is autoimmune, while in dogs it is purely genetic. Tr. 141:3–4. He explained that in humans, "since [he] do[es not] know if [there are] mutations in the receptor or mutations in orexin itself, that the phenotype is driven by something else. And since it[is] linked to HLA-DQ, the most likely explanation in HLA-linked diseases is it[is] an immune disease." Tr. 140:23–141:3. However, Dr. Steinman maintained that humans still need to have the HLA-DQB1*0602 gene to have narcolepsy. Tr. 141:6–9. He stated that "nearly every HLA-linked disease is an immune disease. We[are] talking about multiple sclerosis, rheumatoid arthritis, myasthenia gravis, and the crowning association is in narcolepsy. So it would be really strange if it were[not] immune." Tr. 141:14–18.

Dr. Steinman was asked to discuss the human genetic component of narcolepsy pathogenesis and his research on this issue. Tr. 78:14–22. Dr. Steinman explained that "the crux of the whole matter[is] shown in this Scientific American article[32] that" he published in 1993. Tr. 80:5–7 (citing Pet'r's Ex. 16, ECF No. 19-2). He explained that "the idea of molecular mimicry is that there[is] something in a foreign antigen, like a vaccine to a virus, that is shared with something that[is] on self. And it[is] shown with these modular structures . . . ." Tr. 79:16–19. In the article, Dr. Steinman explained that "*T* cells recognize foreign antigens when they are presented by the

[31] Daniela Latorre et al., *T cells in patients with narcolepsy target self-antigens of hypocretin neurons*, NATURE (2018).
[32] Lawrence Steinman, *Autoimmune Disease*, SCIENTIFIC AMERICAN, Sept. 1993, at 107.

HLA molecules of the immune system. In some people, especially those who have certain HLA types, a foreign antigen may resemble antigen produced by the body. Such molecular mimicry provokes the *T* cells to attack body tissues that contain the self-antigens." Pet'r's Ex. 16 at 4. Dr. Steinman referred to a diagram in the paper, which he said shows that "the molecular structures are in a groove in the HLA molecule. In narcolepsy, it would be a HLA-DQB1*0602. And if there[is] something in the groove that shares enough structural similarity[to the structures shown], . . . it might cause a cross-reaction with self." Tr. 79:24–80:4 (citing Pet'r's Ex. 16 at 4).

Although Dr. Steinman focused his testimony and later expert reports on hypocretin itself, his first two expert reports focused on the hypocretin receptor. In his first expert report, Dr. Steinman stated that "[t]here are molecular mimics of interest between [flu] vaccines containing influenza nucleoprotein[33] and hypocretin receptor[] . . . ." Pet'r's Ex. 14 at 11. He continued that, in a paper he worked on, Ahmed et al.[34] "showed that . . . narcolepsy is linked to the HLA-DQB1*0602 haplotype and dysregulation of the hypocretin ligand-hypocretin receptor pathway." *Id.* (citing Pet'r's Ex. 33, ECF No. 20-9). He noted that "[n]arcolepsy was associated with Pandemrix vaccination (an adjuvanted, influenza pandemic vaccine) and also with infection by influenza virus during the 2009 A(H1N1) [flu] pandemic." *Id.* (citing Pet'r's Ex. 33 at 1). Noting that "very few" narcolepsy cases were identified following a different adjuvanted flu pandemic vaccine, Focetria, Dr. Steinman stated that he and his colleagues "hypothesized that differences between these vaccines (which are derived from inactivated [flu] viral proteins) explain the association of narcolepsy with Pandemrix-vaccinated subjects." *Id.* (citing Pet'r's Ex. 33 at 1). Dr. Steinman stated that "[a] mimic peptide was identified from a surface-exposed region of influenza nucleoprotein A that shared protein residues in common with a fragment of the first extracellular domain of hypocretin receptor 2." *Id.* (citing Pet'r's Ex. 33 at 1). He continued that "[a] significant proportion of sera from HLA-DQB1*0602 haplotype-positive narcoleptic Finnish patients with a history of Pandemrix vaccination (vaccine-associated narcolepsy) contained antibodies to hypocretin receptor 2 compared to sera from nonnarcoleptic individuals with either 2009 A(H1N1) pandemic [flu] infection or history of Focetria vaccination." *Id.* (citing Pet'r's Ex. 33 at 1). He continued that "[a]ntibodies from vaccine-associated narcolepsy sera cross-reacted with both influenza nucleoprotein and hypocretin receptor 2, which was demonstrated by competitive binding using 21-mer peptide (containing the identified nucleoprotein mimic) and 55-mer recombinant peptide (first extracellular domain of hypocretin receptor 2) on cell lines expressing human hypocretin receptor 2." *Id.* at 11–12 (citing Pet'r's Ex. 33 at 1). Dr. Steinman noted that "Mass spectrometry indicated that relative to Pandemrix, Focetria contained 72.7% less influenza nucleoprotein" so "no durable antibody responses to nucleoprotein were detected in sera from Focetria-vaccinated non[-]narcoleptic subjects." *Id.* at 12 (citing Pet'r's Ex. 33 at 1). Dr. Steinman opined that this difference could explain the difference in narcolepsy association between the two vaccines. *Id.*; *see also* Pet'r's Ex. 33 at 1.

Dr. Steinman continued that "[t]he binding site of orexin itself is precisely in the domain that [they] identified as having molecular mimicry with influenza nucleoprotein[.]" Pet'r's Ex. 14

[33] Nucleoprotein is "a substance composed of a simple basic protein, usually a histone or protamine, combined with a nucleic acid." *Nucleoprotein,* DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

[34] Sayed Sohail Ahmed et al. *Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2,* 7(294) SCI. TRANSLATIONAL MED. 1 (2015).

at 12 (citing Pet'r's Ex. 33). Dr. Steinman explained that FluMist, a live-attenuated vaccine, "contains the NP protein that mimics [hypocretin] receptor 2." *Id.* at 14 (citing Pet'r's Ex. 37, ECF No. 21-3). He stated that "[n]ucleoprotein is a central feature of the FluMist vaccine that its manufacturers are advertising . . . ." *Id.* (citing www.flumistquadrivalent.com). Dr. Steinman stated that his theory was that "[t]he nucleoprotein in FluMist cross-reacts with hypocretin receptor 2. An immune response to hypocretin receptor is highly likely to underlie the pathogenesis of narcolepsy." *Id.* at 17. Dr. Steinman continued to support this theory in his second expert report. *See generally* Pet'r's Ex. 43.

However, Dr. Steinman explained that "[s]omething happened in the world of science between [his] first report in 2016 and 2018. A paper [by Latorre et al.] [wa]s published in the top peer-reviewed journal, Nature, from a distinguished group of immunologists, showing that there is an immune response to hypocretin itself, to orexin itself, in [nineteen] out of [nineteen] patients who are narcoleptic." Tr. 72:2–9. Dr. Steinman maintained that "there is still nothing incorrect about the receptor[,]" but his and the scientific community's attention turned "back to orexin[.]" Tr. 72:10–15.

The Latorre study collected blood samples from sixteen patients with hypocretin deficiency and clinical diagnosis of narcolepsy with cataplexy, also known as type 1 narcolepsy. Fourteen of these patients carried the HLA-DQB1*0602 genetic variant. Pet'r's Ex. 49 at 1. They also obtained blood samples from three patients with narcolepsy without cataplexy, or type 2 narcolepsy, and intermediate or normal levels of hypocretin. *Id.* They also collected samples from thirteen controls who had the HLA-DQB1*0602 allele but not narcolepsy. *Id.* The authors used two different methods "to interrogate the T cell repertoire of patients with narcolepsy." *Id.* The authors stated that "[t]he findings of [their] study demonstrate the existence, in patients with narcolepsy, of autoreactive $CD4^+$ and—in some cases—$CD8^+$ T cells that target self-antigens expressed by neurons that produce [hypocretin]." *Id.* at 5. They stated that "[t]he findings of autoreactive $CD4^+$ and $CD8^+$ T cells in narcolepsy raises questions as to their possible pathogenic role." *Id.* at 5. Dr. Steinman wrote that, in the Latorre study, "[t]he epitope GTEFKPRSAL[, among others,] was identified as being a target of cytotoxic T cells found in the cerebrospinal fluid in patients with [t]ype 1 narcolepsy . . . ." Pet'r's Ex. 54 at 10.

Asked to explain the significance of the Latorre article, Dr. Steinman stated that the "article points to the fact that narcoleptic individuals, nearly 100 percent of the time, have immune cells called T cells[35] that react to orexin." Tr. 82:1–6. Dr. Steinman explained that "there[is] mounting evidence [that narcolepsy is an autoimmune disease], and Latorre is certainly one of the shining examples, that there[is] an autoimmune response going on to orexin." Tr. 82:10– 12. Dr. Steinman noted that the paper he worked on in 2015 "point[s] to the receptor[.]" Tr. 82:12–13. Dr. Steinman acknowledged that it is "not proven to certainty, as they say[]" that narcolepsy is an autoimmune condition, "but there[is] really compelling evidence in top peer-reviewed journals where search lights have walked in on an immune response to orexin and its receptor." Tr. 82:14–17. He

[35] T cells, or T lymphocytes, are "the cells primarily responsible for cell-mediated immunity; they originate from lymphoid stem cells that migrate from the bone marrow to the thymus and differentiate under the influence of the thymic hormones thymopoietin and thymosin." *T Lymphocytes*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

continued that he believes "if you asked ten narcolepsy specialists if they had to choose orexin or its receptor, what would they favor, today it would be orexin." Tr. 82:18–20.

Dr. Steinman stated that he performed a BLAST search, which is "a search . . . on a U.S. [g]overnment dataset that asks, is there any commonality between the nucleoprotein in the year of the FluMist vaccine and orexin." Tr. 73:4–7. Dr. Steinman stated that the BLAST search took him "to one and only one spot." Tr. 73:7–8. He continued that "the one and only one spot it t[ook] [him] to on the BLAST search is exactly where, in one of Latorre's figures, there[is] an immune cell called a T cell in the spinal fluid which attacks the very same region." Tr. 73:8–12. Dr. Steinman explained that his BLAST search on the nucleoprotein from the FluMist vaccine V.H. received showed that "orexin shared molecular similarity with the components of V.H.'s vaccine in the nucleoprotein, not in the [hemagglutinin],[36] not in the neuraminidase,[37] but in the nucleoprotein, which is in the vaccine." Tr. 81:1–7. Dr. Steinman stated that the FluMist vaccine is a "live virus vaccine. It has the whole virus." Tr. 82:25–83:1. He continued that the company selling FluMist included in its promotional materials four proteins contained in the vaccine: "[t]he [hemagglutinin], the neuraminidase, the nucleoprotein, and the two proteins called M1 and M2." Tr. 83:2–6. Dr. Steinman explained that these proteins are responsible for "attract[ing] the immune system." Tr. 83:6–8.

Dr. Steinman explained that after identifying the viral strains in the FluMist vaccine, he ideally would "like to get an individual's blood and do all the things that we did in the 2015 Ahmed paper[]" but noted that this option is unavailable in vaccine cases. Tr. 84:17–22 (citing Pet'r's Ex. 33). Dr. Steinman continued that he therefore "did a BLAST search of various influenza B components to see whether they had any molecular mimicry with orexin." Tr. 84:23–25. Dr. Steinman explained that, when he performs a BLAST search, he is looking to see if there are "any similarities in some region, any region, of the two proteins [being compared] that might help explain how an immune response to one protein could trigger an immune response to self." Tr. 85:16–22. Dr. Steinman indicated that this is referred to as "sequence homology." Tr. 86:1–3.

Dr. Steinman stated that his BLAST search in this case showed "a [five-]out-of[-ten] identity [of amino acids], in one and only one area, and it was the same [region of the molecule] that appeared in Latorre in one of the figures as an example of what the immune system in a narcoleptic patient responds to." Tr. 87:8–17. He explained that his BLAST search showed that "[t]he sequence GTEFKPRSAL contains [five] identical amino acids out of [ten] amino acids shared between orexin and the nucleoproteins of both the Influenza B Yamagata and Victoria components of the 2012 FluMist vaccine." Pet'r's Ex. 54 at 10. Dr. Steinman noted that the lot release[38] indicates that a different influenza B component, B/Wisconsin/1/2010, was also present in the 2012-13 FluMist vaccine. *Id.* (citing Pet'r's Ex. 55 at 1.) However, he noted that his BLAST search for this component still contained the same molecular mimic. *Id.*

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[36] Hemagglutinin is "an agglutin, e.g., an antibody or lectin, that agglutinates erythrocytes." *Hemagglutinin*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

[37] Neuraminidase is "an enzyme of the hydrolase class that catalyzes the cleavage of glucosidic linkages between a sialic acid residue and a hexose or hexosamine residue at the nonreducing terminal of oligosaccharides in glycoproteins, glycolipids, and proteoglycans." *Neuraminidase*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

[38] FDA, *Lot Release (Biologics): Influenza Virus Vaccine for the 2012-2013 Season.*

When asked if five out of ten was enough to induce molecular mimicry, Dr. Steinman stated that his "laboratory, in collaboration with some other laboratories, showed that in a well-recognized animal model, what was sufficient was [five] out of [twelve] . . . they need not be consecutive amino acids." Tr. 87:20–24. Dr. Steinman stated that this was also supported by Root-Bernstein,[39] who "also used [five] out of [ten] and showed some molecular mimics as well[]" when exploring molecular mimicry in the context of human rheumatic heart disease. Tr. 87:24–88:3 (citing Pet'r's Ex. 68 at 1, ECF No. 69-3 (stating that "[s]imilarities [in this study] were considered to be significant if a sequence contained at least [five] identical amino acids in [ten]")).

Dr. Steinman relied on the Gautam articles[40] he was involved in. *See* Tr. 89–90 (citing Pet'r's Exs. 25–26, ECF Nos. 20-1–20-2). Dr. Steinman explained that they "injected animals to see if, [] say, [five] out of [ten], or [five] out of [twelve], could cause paralysis in a model of multiple sclerosis called [experimental autoimmune encephalomyelitis ("EAE")]." Tr. 89:19–21. He noted that these were myelin, rather than narcolepsy, molecular mimics. Tr. 89:22–23. Dr. Steinman acknowledged that this study utilized an adjuvant because "[they] wanted to see something that happened with high fidelity when [they] worked with [ten] or [twenty] animals, not 200,000 animals, because [he] can[not] do that." Tr. 89:25–90:4. Dr. Steinman stated that "the [five] out of [ten] identity with the myelin protein was enough to cause an animal to get paralyzed, but [he] did have to use an adjuvant because [he] did[not] want to inject a few hundred thousand animals to see one that got sick[] . . . ." Tr. 90:5–11. Dr. Steinman averred that the use of an adjuvant did not detract from his conclusion that five identical amino acids were sufficient "if you look at it from how much homology do you need to get that paralysis." Tr. 90:12–17. He concluded that his "point is all [he] needed was [five] out of [ten] identities and the animals still got paralyzed." Tr. 90:23–25. Dr. Steinman acknowledged that an animal model testing experimentally induced narcolepsy does not exist yet. Pet'r's Ex. 54 at 6. Using the Gautam articles, Dr. Steinman opined that "at least five identical amino acids in a consecutive stretch of [twelve] amino acids situated in the regions where the two proteins align without gaps [] would be sufficient to produce clinical neuroinflammation." *Id.*

On cross-examination, Dr. Steinman was asked about the statement in the Silvanovich[41] article he submitted that "[s]earches for short amino acid sequence matches of eight amino acids or fewer, to identify proteins as potential cross-reactive allergens, is a product of chance and adds little value to allergy assessments for newly expressed proteins." Pet'r's Ex. 58 at 1, ECF No. 86-4; Tr. 132:18–24. Dr. Steinman disagreed with this statement. Tr. 134:14–24. Dr. Steinman explained that this case does not involve an allergic response, that there are many cases in which he finds no homologies, and that Silvanovich "sort of refutes himself[]" because he states that the

[39] Robert Root-Bernstein, *Rethinking molecular mimicry in rheumatic heart disease and autoimmune myocarditis: laminin, collagen IV, CAR, and BIAR as initial targets of disease* 2 FRONTIERS IN PEDIATRICS 85 (2014).

[40] Anand M. Gautam et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J. IMMUNOL 60 (1998); Anand M. Gautam et al., *Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: Implications in induction of autoimmunity*, 91 PROC. NATL. ACAD. SCI. USA 767 (1994).

[41] Andre Silvanovich et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity*, 90(1) TOXICOLOGICAL SCIENCES 252 (2006).

BLAST search is the preferred tool compared to sliding window searches. Tr. 133:1–9; Pet'r's Ex. 58 at 7 ("Thus, for large proteins and an expanding allergen database, a FASTA or BLAST bioinformatics search appears to be the optimum method for identifying potential similarities between newly expressed proteins and known allergens."). Silvanovich et al. stated that "[b]ioinformatic analyses based on FASTA or BLAST algorithms provide a measure of reliability by providing cut-offs (35% identity over at least 80 amino acids), above which significant IgE cross reactivity may be expected to occur []. In the absence of a ranking, matches with bona fide IgE-binding motifs are indistinguishable from false-positive matches in a sliding window search." Pet'r's Ex. 58 at 7.

Dr. Steinman opined that "Petitioner's efforts to demonstrate that there is a molecular mimic between the components of the FluMist 2012 vaccine and an orexin peptide actually targeted in humans with type 1 narcolepsy is about as close to discovering the 'smoking gun' as modern science can provide." Pet'r's Ex. 54 at 13.

In addition to the BLAST search, Dr. Steinman also used the Immune Epitope Database ("IEDB"), which "catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity, and transplantation." Pet'r's Ex. 65 at 10 (quoting http://www.iedb.org/home_v3.php). Dr. Steinman noted that the GTEFKPRSAL epitope was "identified independently at the IEDB[.]" *Id.* Dr. Steinman explained that "GTEFKPRSAL with [nine] of [ten] identical amino acids appears in the search [] from IEDB. The filtration process correctly identified this epitope in the nucleoprotein, a protein with 560 amino acids." *Id.* at 11. Dr. Steinman described it as "remarkable" "that the filtration process focused on this portion of nucleoprotein[]" and "that this region was identified as a target of the immune response in narcolepsy[in the Latorre article.]" *Id.* at 11–12. He also explained that the experiments relied on in the IEDB "were done on actual humans." Tr. 92:20–25.

Dr. Steinman explained that he "started out with a BLAST search[] . . . then filter[ed] it the with the . . . Gautam and Root-Bernstein criteria, and then [he] look[ed] at other databases to see whether this has been shown by others in doing experiments on humans. And if it comes out at the end of the funnel, the theory is ever more refined and important, in [his] opinion." Tr. 93: 12–19.

Latorre et al. found "[n]o T cell cross-reactivity with influenza antigens[.]" Pet'r's Ex. 49 at 2. However, Dr. Steinman noted that the study used the Influvac vaccine rather than FluMist. Pet'r's Ex. 54 at 12; *see also* Pet'r's Ex. 49 at 7 (indicating that Latorre et al. used Influvac). Dr. Steinman concluded that it was "extremely unlikely that [Latorre et al.] used the 2012 FluMist vaccine." Pet'r's Ex. 54 at 13. Further, the authors indicated that "none of the [hypocretin] or TRIB2-specific T cell clones proliferated in response to influenza vaccine containing A/California/7/2009 H1N1 or to CA09 H1 haemagglutinin []." Pet'r's Ex. 49 at 2. Dr. Steinman acknowledged that his BLAST search showed that "[t]he H1N1 hemagglutinin does not cross-react to orexin . . . ." Pet'r's Ex. 54 at 12. Dr. Steinman later addressed the Deerhake et al. article,[42] which stated that "the discovery of autoreactive T cells identified in the [Latorre] study did not support the molecular-mimicry hypothesis in narcolepsy. Specifically, H1N1 vaccine components

[42] M. Elizabeth Deerhake et al., *Are Neuropeptide-Reactive T Cells behind Narcolepsy?*, 49 IMMUNITY 796 (2018).

did not induce proliferation of any of the identified [hypocretin] or TRIB2-specific T cell clones [].” Resp’t’s Ex. S, Tab 4, at 2, ECF No. 62-5. Dr. Steinman stated that he looked into the Influvac vaccine and discovered on the internet that the vaccine has hemagglutinin and neuraminidase but not nucleoprotein. Tr. 103:9–18. Dr. Steinman stated that Deerhake et al.’s “conclusion about the reputation of molecular mimicry cannot stand because the vaccine they used does not have where the mimic is.” Tr. 103:19–24. Deerhake et al. also suggested that the hypocretin specific “T cells [found by Latorre] might be a secondary consequence of neuronal damage in narcolepsy and might not play a causal role.” Resp’t’s Ex. S, Tab 4, at 2.

When asked if “sequence similarity alone is sufficient to trigger autoimmunity via molecular mimicry[,]” Dr. Steinman said no. Tr. 107:22–25. He stated that “[f]irst of all, you[would] have to have the [HLA-DQB1*0602] gene[.]” Tr. 107:25–108:1. He noted that he relied on other information, including that the area involved “is an area that[has] been studied not only in [his] BLAST searches, but by others on the IEDB and by Latorre.” Tr. 108:1–14.

Dr. Steinman addressed the notion that peptide sharing between viral and human proteomes is widespread. *See* Tr. 111–13. Dr. Steinman noted that despite the general existence of “massive amounts of mimicry,” he did not find massive amounts in this case. Tr. 112:9–12. Instead, he “found only one area of mimicry between nucleoprotein . . . found in this vaccine and orexin, and it happened to be the same area that Latorre showed in [HLA-DQB1*0602] patients.” Tr. 112:12–15. Addressing that Dr. MacGinnitie found other matches, such as zinc finger protein, overlapped with the peptide at issue, Dr. Steinman noted that “we do[not] immunize with [zinc finger proteins.” Tr. 113:6–25.

Dr. Steinman addressed epidemiological studies, particularly the Duffy study,[43] involving narcolepsy and flu vaccines. *See* Tr. 97–99. Dr. Steinman noted that “the quality of the data [] collect[ed in an epidemiological study], especially with a control group, can determine [the] outcome.” Tr. 98:22–24. Dr. Steinman opined that the “comparator group[]” as well as the rarity of vaccine reactions should be considered when evaluating an epidemiological study. *See* Tr. 99:2–6. Duffy et al. completed “a population-based cohort study in the Vaccine Safety Datalink with an annual population of more than 8.5 million people.” Resp’t’s Ex. A, Tab 17, at 1. The researchers identified “[a]ll persons younger than [thirty] who received a 2009 pandemic or a 2010-2011 seasonal [flu] vaccine [].” *Id.* Duffy et al. followed 650,995 people who received flu vaccines during the 2009 pandemic and 870,530 people who received flu vaccines during the 2010–2011 flu season. *Id.* The researchers searched patients’ medical visit histories to locate new narcolepsy diagnoses through 2011. *Id.* The researchers then “compared the observed number of cases after vaccination to the number expected to occur by chance alone.” *Id.* Duffy et al. concluded that “[flu] vaccines containing the A(H1N1)pdm09 virus strain used in the United States were not associated with an increased risk of narcolepsy. Vaccination with the influenza A(H1N1)pdm09 vaccine viral antigens does not appear to be sufficient by itself to increase the incidence of narcolepsy in a population.” *Id.*

Duffy et al. identified sixteen cases of chart-confirmed incident diagnoses of narcolepsy across the various types of flu vaccines they evaluated. *Id.* at 1, 3. The onset in these sixteen cases

[43] Jonathan Duffy et al., *Narcolepsy and influenza A(H1N1) pandemic 2009 vaccination in the United States*, 83 NEUROLOGY 1823 (2014).

ranged from four to thirty-six months post vaccination, and the authors stated that "[t]he distributions do not suggest a cluster of cases after the 2009 pandemic vaccination program." *Id.* at 3–4. The authors noted that "[they] found fewer chart-confirmed cases of narcolepsy with symptom onset in the [six] months after receipt of [flu] vaccine than would have been expected by chance alone." *Id.* at 4. The paper includes a chart breaking down the results among the various vaccines studied and age groups within 180 days post vaccination and compares the results to the expected incidence rate per 100,000 persons. *Id.* at 5. The researchers followed recipients of four different types of vaccines. *See id.* For the 2009 pandemic, the researchers followed 439,031 people who received monovalent inactivated vaccines ("MIVs") and 211,964 people who received monovalent live attenuated vaccines ("MLAIVs"). *Id.* For the 2010-2011 flu season, the researchers followed 740,982 people who received trivalent inactivated vaccines ("TIVs") and 129,548 who received LAIVs. *Id.* The researchers found only two cases of narcolepsy within 180 days post vaccination, which were in ten to nineteen-year-olds who received TIVs. *Id.* The authors noted the expected incidence rates: 1.01 cases out of 100,000 individuals under age ten, 3.84 out of 100,000 individuals between ages ten and nineteen, and 1.84 cases out of 100,000 individuals between ages twenty and twenty-nine. *Id.* The group that received the LAIV, with 129,548 recipients, was the smallest of the vaccines studied. *See id.* 81,410 recipients under the age of ten who received the LAIV were studied, and zero new narcolepsy cases were identified within 180 days. *Id.* The expected numbers of cases for this age group would have been 0.4 out of 81,410. *Id.* In total, the authors identified zero cases of narcolepsy within 180 days of LAIV vaccination even though 1.26 would have been expected per the 129,548 LAIV cases that were followed. *Id.* Across the vaccines and age groups studied and sixteen chart-confirmed cases, "[n]one [of the patients] had their symptom onset during the 180 days after receipt of a 2009 pandemic vaccine compared with 6.52 expected, and [two] had onset after a 2010–2011 seasonal vaccine compared with 8.83 expected." *Id.* at 1.

Noting "the relative paucity of [HLA-DQB1*0602] patients in the [United States,]" Dr. Steinman opined that "the failure to observe narcolepsy within FluMist in the Duffy study[is] subject to the limitations of a relatively small sample size for such a rare event." Pet'r's Ex. 43 at 10. Dr. Steinman noted that Duffy et al. shared his reservations because they noted that "[they] based [their] expected number of cases on the only chart-confirmed incidence rate estimates published to date, which might not reflect the base-line incidence in [their] study population." *Id.* at 10–11 (quoting Resp't's Ex. A, Tab 17 at 4). Duffy et al. continued that "[h]owever, even if [they] assumed that the true baseline incidence was one order of magnitude less, the zero cases observed in [their] 2009 pandemic vaccinated cohort would still be less than the 0.652 cases expected." *Id.* at 11 (quoting Resp't's Ex. A, Tab 17 at 4). Dr. Steinman was also critical of the Duffy study because "the authors assessed the incidence of narcolepsy in a population that was followed for approximately [thirty] years for its background rate but followed the post-vaccine population for [six] months (or a year). That created an artificially high background rate (apples) which Duffy compared to an artificially low post-vaccine rate (oranges)." Pet'r's Ex. 54 at 14. Dr. Steinman compared Duffy's background rate to that used in the Montplaisir article, which found an increased risk of narcolepsy in people residing in Quebec who received an inactivated and adjuvanted H1N1 vaccine similar to Pandemrix.[44] *Id.* (citing Pet'r's Ex. 61, ECF No. 59-7). Dr. Steinman explained that the Montplaisir study "used the data the authors collected in Quebec after

[44] Jacques Montplaisir et al, *Risk of Narcolepsy Associated with Inactivated Adjuvanted (AS03) A/H1N1 (2009) Pandemic Influenza Vaccine in Quebec*, 9(9) PLOS ONE 1 (2014).

the H1N1 pandemic and H1N1 vaccination. The background rate of narcolepsy (based on a [six] month to year follow up) in Quebec . . . was 1/10 that in Rochester [C]ounty, Minnesota (based on the roughly [thirty] year follow-up in the study that Duffy used for its background rate)." Pet'r's Ex. 54 at 14. Dr. Steinman stated that he does not "think epidemiology can tell us about FluMist and narcolepsy when these events are so rare." Tr. 100:12–14.

I asked Dr. Steinman to explain why he did not think the right control group was used in the Duffy study. Tr. 151:11–13. Dr. Steinman stated that "they used Rochester, Olmstead County, and the rates are much higher in Quebec than a more contemporary setting. So [he] think[s] you could have just done comparisons against several different control groups and then said, you can make different conclusions based on different control groups." Tr. 151:14–19. Dr. Steinman averred that "[i]f you used Montplaisir in Quebec with the background rate it shows in there, then you would construe the fact that narcolepsy could be associated with H1N1." Tr. 152:6–9. He explained that a different control group would lead to a different conclusion. Tr. 152:16–19.

Dr. Steinman was asked to address an abstract[45] he submitted claiming an increase in narcolepsy in the United States following the 2009 H1N1 pandemic. Tr. 100:18–21. Dr. Steinman stated that the authors of this abstract "show that there is a significant increase in the number of childhood narcolepsy patterns that are similar to what was seen with the 2009 H1N1 pandemic in the United States." Tr. 102:6–9 (citing Pet'r's Ex. 62, ECF No. 59-8).

On cross-examination, Dr. Steinman was asked whether he would support causation in this case even if the Latorre paper were unavailable. Tr. 122:11–13. Dr. Steinman stated that he would still support it based on the Ahmed paper, even though the Ahmed paper does not concern the nucleoprotein of influenza B. Tr. 122:14–20. Dr. Steinman clarified that the FluMist vaccine contains influenza A and influenza B and that he relied "on La[t]orre because it[is] closer to what [he] used as the term the 'smoking gun.'" Tr. 122:24–123:2. Dr. Steinman acknowledged that Ahmed and Latorre both concerned influenza A components while his theory regarding nucleoprotein and orexin pertains to influenza B. Tr. 123:3–12. However, Dr. Steinman maintained that "Ahmed does[not] go away because [he is] using Latorre." Tr. 123:18. He stated that "the nucleoproteins are not dissimilar between influenza A and B, and they[are] not dissimilar over the prior years. They still are nucleoproteins [in the flu] vaccine." Tr. 123:19–22.

Respondent asked Dr. Steinman to clarify his statement in his third expert report that he was "no longer focusing on the cross-reactivity between hypocretin receptor 2 and the nucleoprotein in [the] Pandemrix vaccine." Tr. 125:17–21; Pet'r's Ex. 54 at 15. Dr. Steinman stated that although he shifted focus to orexin rather than its receptor, he was "not taking the immune response to the receptor off the table." Tr. 125:22–126:2. Dr. Steinman noted that narcoleptic dogs have a mutation in the receptor and do not, as far as he knows, experience an immune response to the nucleoprotein. *See* Tr. 126:2–7. Dr. Steinman stated that if he had to choose between the receptor and orexin for his theory, "it[is] more compelling with orexin, but [he does not] want to have to choose one." Tr. 127:2–4.

[45] Simakajornboon N et al., *Increased Cases of Childhood Narcolepsy after the 2009 H1N1 Pandemics: Preliminary Data from The Pediatric Working Group of The Sleep Research Network* 40 SLEEP A337 (2017).

Noting that Dr. Steinman presented two theories in this case, I asked him to explain how "the introduction of cross-reactivity, as it relates to orexin[] . . . fit[s] into [his] pre-existing theory, if [he] want[s] me to consider it all such that I can apply it to this case." Tr. 157:25–158:4. Dr. Steinman stated that "it seems to [him] that it would be much easier, [] to go with the molecular mimicry between orexin and the FluMist vaccine, and just go with [his latter three reports. He] would say [not to] worry about . . . the receptor, just worry about orexin." Tr. 158:5–14. Dr. Steinman averred that his later theory is his best theory in this case. Tr. 158:15–16. On redirect, Dr. Steinman clarified that his theories differed in that he was looking at two different candidates for the source of molecular mimicry. Tr. 159:14–17.

Respondent asked Dr. Steinman if he did a BLAST search for the influenza A components of FluMist. Tr. 128:12–14. Dr. Steinman stated that he did not recall if he did. Tr. 128:15. Dr. Steinman acknowledged that H1N1 is an influenza A strain. Tr. 128:20–129:1. Respondent asked Dr. Steinman why, since the epidemiological data regarding Pandemrix concerned H1N1, he did not think it was important to do a BLAST search for the influenza A components. Tr. 129:2–5. In response, Dr. Steinman noted that the "H" and "N" in "H1N1" stand for hemagglutinin and neuraminidase, respectively. Tr. 129:6–8. However, "[b]oth in Ahmed and Latorre, the mimic that [he] found relevant was nucleoprotein." Tr. 128:8–9. Dr. Steinman acknowledged that he had not found "molecular mimicry between the nucleoprotein in the Pandemrix vaccine and hypocretin[]" even though epidemiology linked narcolepsy and Pandemrix. Tr. 138:3–13.

When reminded that he stated in his report that H1N1 hemagglutinin does not cross-react with orexin, Dr. Steinman recalled performing a BLAST search for influenza A. Tr. 129:12–16. Dr. Steinman asserted that this does not undermine his theory regarding the hypocretin receptor. Tr. 129:21–25. Dr. Steinman acknowledged that he is not aware of medical literature relating influenza B vaccination or infection to narcolepsy pathogenesis. Tr. 131:10–13.

To summarize his theory, Dr. Steinman stated that "in [] FluMist[,] there[is] a component which shares molecular similarity with the hypocretin molecule itself." Tr. 75:2–4. Dr. Steinman maintained that "the science [in his first report] is still valid, and the region in [his] first report is exactly where hypocretin binds the receptor." Tr. 75:6–9. He continued that "[t]he receptor is vital in the whole story, but" if he had to choose, his favored, based on the literature, "is that there[is] a molecular mimic in FluMist which could cause narcolepsy if an individual reacted to that region. And that region is known to occur in narcoleptic patients based on [the article by] Latorre." Tr. 75:10–16. Dr. Steinman explained that the BLAST search did not "take [him] everywhere on the orexin molecule, it took [him] directly to the same . . . epitope that was shown in [the] Latorre [article], and that was in a cell in the spinal fluid of an individual with narcolepsy. That[is] about as close as we can get to . . . the actual neurons that are destroyed in that brain." Tr. 259:24–260:8.

Discussing V.H.'s history prior to his September 2012 FluMist vaccination, Dr. Steinman opined that V.H. had no previous medical issues worth addressing prior to this vaccination. Tr. 64:23–65:1. Dr. Steinman found it significant that V.H. received a FluMist vaccine previously and opined that V.H.'s second FluMist vaccine "could have triggered a recall response, a more vigorous response than the first one." Tr. 65:12–16.

Dr. Steinman addressed that there had been some discussion during the hearing about the timing of the onset of V.H.'s narcolepsy post vaccination. Tr. 65:22–23. However, he maintained that "it was approximately a month . . . maybe two months, but . . . this is a time frame that[is] pretty widely accepted by [Dr. Steinman] as being in the target zone of where a vaccine response, at least for a temporal association, is reasonable." Tr. 65:22–66:7. Dr. Steinman opined that Petitioner's description of V.H.'s symptoms during V.H.'s appointment with PA Hansen in January of 2013 "was consistent with the development of narcolepsy." Tr. 66:7–15. Dr. Steinman averred that following V.H.'s symptoms and sleep testing, the confirmation that he was positive for HLA-DQB1*0602 "clinched" V.H.'s narcolepsy diagnosis. *See* Tr. 67–68:1. Dr. Steinman stated that he "[a] hundred percent" agreed with V.H.'s narcolepsy with cataplexy diagnosis. Tr. 68:17–19.

Dr. Steinman stated that an onset of narcolepsy four to six weeks post vaccination is "a very appropriate time frame." Tr. 116:1–4. He explained that Petitioner's reaction was "likely a recall response, he had FluMist before, and that fits with what we know about recall responses." Tr. 116:4–6. Dr. Steinman explained that a recall response can occur within twenty-four to forty-eight hours of a second vaccination but normally "peak in a few weeks." Tr. 143:24–144:2. Dr. Steinman cited an article by Wrammert et al.,[46] which he claimed "showed that a recall response to influenza vaccine peaks around [seven] days post[] vaccination []." Pet'r's Ex. 14 at 17 (citing Pet'r's Ex. 41, ECF No. 21-7). Wrammert et al. stated that "[f]or [flu] virus, annual vaccinations are given to maintain protective levels of antibody against the currently circulating strains." Pet'r's Ex. 41 at 1. Wrammert et al. stated that their "results showing the rapidity of the antibody response after vaccination and the high affinity of the antibodies produced strongly suggests that the recall response could also play a role in protective immunity." *Id.* at 4.

Dr. Steinman also stated that "[t]he timing [] in this case, with the onset of sleep disturbance in approximately one month post[] vaccination is in line with what we know about the immunology of a response to influenza vaccine and to the onset of narcolepsy-cataplexy following natural infection or following [the] Pandemrix vaccine." Pet'r's Ex. 14 at 17. He provided an article by Ahmed et al.,[47] that he was involved in. Ahmed et al. stated that the increased risk of narcolepsy following adjuvanted H1N1 vaccines in Finland involved narcolepsy with an onset of approximately two months post vaccination. Pet'r's Ex. 15 at 3, ECF No. 19-1. Ahmed et al. also cited the Han[48] study, which was also submitted in this case. *Id.* (citing Pet'r's Ex. 64, ECF No. 19-1). Ahmed et al. stated "[t]he time to narcolepsy onset [in the Han study] following [H1N1] flu infection was six months." *Id.* Han et al. concluded that "[i]n China, narcolepsy onset is highly correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza." Pet'r's Ex. 64 at 1. They noted that "[c]ross-correlation indicated a significant [five]- to [seven]-month delay between the seasonal peak in influenza/cold or H1N1 infections and peak in narcolepsy onset occurrences." *Id.* Dr. Steinman also indicated that the Han study is significant

[46] Jens Wrammert et al., *Rapid cloning of high affinity human monoclonal antibodies against influenza virus*, 453(7195) NATURE 667 (2008).
[47] S. Sohail Ahmed et al., *Narcolepsy, 2009 A(H1N1) pandemic influenza and pandemic influenza vaccinations: What is known and unknown about the neurological disorder, the role of autoimmunity, and vaccine adjuvants*, 50 J. AUTOIMMUNITY 1 (2014).
[48] Fang Han et al., *Narcolepsy Onset is Seasonal and Increased following the 2009 H1N1 Pandemic in China*, 70 ANN. NEUROL. 410 (2011).

because it "show[ed] that the association of [flu] and narcolepsy is not exclusively linked to A/H1N1 strains[.]" Pet'r's Ex. 54 at 17 (citing Pet'r's Ex. 64 at 1). Furthermore, Ahmed et al. noted that "[d]ue to their similarity in structure with the natural virus or bacteria, live vaccines could induce molecular mimicry similar to that associated with the natural infection []." Pet'r's Ex. 15 at 5. When Dr. Steinman was asked about the timing in the research he was involved in regarding narcolepsy following the Pandemrix vaccine, he stated that the finding was "[m]onths to a lot longer." Tr. 116:18–24.

When asked whether the medical records suggested any potential cause of V.H.'s narcolepsy besides the FluMist vaccine, Dr. Steinman stated that there was "[n]othing else that pops in [his] mind. No significant viral-like illness . . . ." Tr. 68:2–6. He noted that there is "a lot of literature . . . about H1N1 being associated with higher incidence of narcolepsy in the calendar months when [flu] H1N1 infections are more prevalent." Tr. 68:7–12.

Dr. Steinman was asked to address Respondent's argument that the record does not show evidence that V.H. had an autoimmune reaction. Tr. 114:17–20. Dr. Steinman acknowledged that "there[is] nothing in the medical record[.]" Tr. 115:2. He added, "had we done all the sophisticated tests that we[are] capable of running[] . . . and did a Latorre type of investigation, we might have found it, but it all depends on what we were looking for or whether there was a search for it. These are not common tests or research tests." Tr. 114:21–115:1. Dr. Steinman stated that "we might be running Latorre type tests on narcoleptic patients in the not-too-distant future. But . . . there[is] not any evidence that such a test was done way back in the year 2013." Tr. 115:8–12. Dr. Steinman clarified that he would not expect a narcolepsy patient's medical records to indicate inflammation. Tr. 115:13–15.

Respondent asked Dr. Steinman whether they could "agree that type 1 narcolepsy is not associated with findings of neuroinflammation[.]" Tr. 134:25–135:1. Dr. Steinman disagreed and later said "[i]t depends." Tr. 135:2, 137:3. He continued that "[i]f we only could see what . . . that pathway in the brain looked like early in disease[. I]f we were dealing with a skin disease or liver disease or a kidney disease, we would biopsy it." Tr. 135:2–6. He explained that "we do[not] biopsy brains very easily, very readily, and this would cause a significant amount of damage." Tr. 135:6–8. Dr. Steinman continued that if doctors were able to more closely examine the brain in narcolepsy and other neurodegenerative diseases, they "might see the criminal immune system attacking itself. And these are inaccessible[,] and it may be [a] hit and run. They may hit it and the neurons are gone and then you do[not] get to see them." Tr. 135:9–16. Respondent asked Dr. Steinman whether he agreed with the Scammell article[49] that "no signs of inflammation are detected in cerebrospinal fluid[50] or seen on magnetic resonance imaging ("MRI") in people with narcolepsy." Tr. 137:10–14. Dr. Steinman agreed with this statement. Tr. 137:15–16; Resp't's Ex. A, Tab 2 at 5, ECF No. 47-3.

[49] Thomas E. Scammell, *Narcolepsy*, 373(27) N. ENG. J. MED. 2654 (2015).

[50] Cerebrospinal fluid is "the fluid contained within the four ventricles of the brain, the subarachnoid space, and the central canal of the spinal cord[.]" *Liquor Cerebrospinalis*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

I asked Dr. Steinman if, in a rechallenge event, there would be an immune response at the time of the first vaccination. Tr. 141:19–24. Dr. Steinman responded that "there may have been an insufficient immune response after the first vaccine." Tr. 141:25–142:1. He continued that he "would[not] expect an immediate recall response." Tr. 142:4–5. He stated that "[a] really good response to something that cross-reacts with orexin would be just the right time frame for V.H. to have developed the really fulminant problems that [Ms. Henkel] shared with us and that are in the medical records. So a recall response could really get mustard [sic] with a few weeks to a month or a month and a half." Tr. 142:8–14.

I also asked Dr. Steinman how he can argue that V.H. experienced a recall response after the second vaccination when there is no evidence of an acute immune response to the first vaccination. Tr. 143:20–23. Dr. Steinman opined that there was evidence of a recall in this case "because it was [V.H.'s] second shot and it took a few weeks to a month or so to have the . . . manifestations apparent in narcolepsy. There may have been subclinical manifestations earlier, but that[is] why [Dr. Steinman] think[s] it fits wonderfully with the manifestation of a recall response." Tr. 144:5–10. Dr. Steinman explained that "[w]hat happens in the recall response is that you start very quickly making antibodies and T cell responses, but the antibodies even become stronger binding antibodies over a period of days to weeks." Tr. 145:3–6. Dr. Steinman conceded that he had no evidence that a recall response occurred in this case besides the manifestation of V.H.'s narcolepsy. Tr. 146:3–6. Dr. Steinman averred, however, that "a second vaccine, by definition, triggers a recall response[]" and that a recall response is almost always present if a patient suffers a vaccine injury after receiving a vaccine more than once. Tr. 146:10–16.

I also asked Dr. Steinman to explain how V.H. would have experienced a systemic reaction after a vaccination localized in the nasal cavity. Tr. 147:6–10. Dr. Steinman explained that "the FluMist goes into the nose, immune cells called macrophages . . . take it to the regional lymph nodes . . in the upper respiratory tract. There we start developing, since this was a second immunization, the recall response at the T cell and B cell level." Tr. 147:11–18. Dr. Steinman continued that the "regional lymph nodes, which are outside, the brain[]" are targeted by the T and B cells.[51] Tr. 147:19–24. I asked Dr. Steinman to explain how the cells are able to cross into the brain. Tr. 148:12–13. Dr. Steinman responded, "[w]ell, they do." Tr. 148:14. He explained that "there are receptors called integrins. They[are] like Velcro molecules on T cells and B cells that bind to the endothelium on blood vessels and allow the T cells and B cells to cross the blood vessels called diapedesis, and then they go on patrol." Tr. 17–21. Dr. Steinman explained that when the integrins are blocked, "people get these horrible, rare diseases that show what happens when we do[not] have immune surveillance." Tr. 148:22–25. Dr. Steinman noted that "it[is] a really cutting-edge question for which there are some answers, but that[is] the best [he] can do." Tr. 149:4–6. Dr. Steinman stated that while this mechanism has not been studied in regard to narcolepsy, it has been applied to multiple sclerosis and type 1 diabetes. Tr. 149:23–150:5.

2. Respondent's Expert, Dr. MacGinnitie

[51] B cells, or B lymphocytes, are "the cells primarily responsible for humoral immunity, the precursors of antibody-producing cells (plasma cells)." *B Lymphocytes*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 6, 2022).

Dr. MacGinnitie testified at the hearing and supplied three expert reports. *See* Resp't's Exs. A, S; Resp't's Ex. V, ECF No. 70-1; Tr. 194–257. Although he expressed some skepticism, Dr. MacGinnitie opined that narcolepsy is "more likely than not . . . an autoimmune disease." Tr. 199:13–17. Dr. MacGinnitie stated that Latorre "definitely" supports that type 1 narcolepsy is autoimmune. Tr. 218:21–23. He explained that "type 1 narcolepsy is due to these [sic] loss of neurons that secrete hypocretin. The arm of the immune system that typically kills cells are T cells, and so the fact that there[is] a T cell response against hypocretin would be evidence for" autoimmunity "and provide the mechanism [of autoimmunity]." Tr. 218:24–219:5.

Regarding Dr. Steinman's revised theory, Dr. MacGinnitie remarked that "it[is] really a completely new theory, and [he does not] think that the epidemiological evidence from Pandemrix is at all related to this because it[is] a different influenza strain." Tr. 214:15–18. Further, Dr. MacGinnitie "emphasize[d] how tenuous [this theory] becomes" in light of the [Systemic Observational Method of Narcolepsy and Influenza Immunizations Assessment ("SOMNIA")] study, which is discussed in an article by Weibel et al.,[52] because "[i]t is now clear that, at best, narcolepsy after [flu] vaccination is only associated with a specific vaccine in a specific region." Resp't's Ex. S at 3 (citing Resp't's Ex. S, Tab 2, ECF No. 62-3). He continued that "[a]lternatively, any increased rate may either artefactual [sic] or only occurs in the setting of wild-type [H1N1] infection." *Id.*

Dr. MacGinnitie was asked if the destruction of hypocretin implicated in Dr. Steinman's theory would "result in the loss of neurons that is the hallmark of narcolepsy[.]" Tr. 214:19–21. Dr. MacGinnitie averred that:

> the function of the HLA molecules is to present peptides . . . on the surface of the cells, and so certainly the hypocretin peptides could be presented on the surface of the neurons that produce them, and that could make them susceptible to an autoimmune attack if there were T cells that recognized that peptide in the context of that HLA.

Tr. 214:22–215:4.

Dr. MacGinnitie opined that it was insignificant that Dr. Steinman found a five-out-of-ten match between orexin and the nucleoprotein in the vaccine's influenza B component. Tr. 215:19–24. Dr. MacGinnitie disagreed with Dr. Steinman's assessment of the Silvanovich quote regarding short amino acid sequences. Tr. 217. Dr. MacGinnitie asserted that "the general point remains that looking for modest degrees of homology in short stretches is subject to[] . . . chance findings[.]" Tr. 217:14–16. Dr. MacGinnitie stated that "there[is] actually this statistical technique built into BLAST called the expect value that helps correct for that, and the searches displayed in [Dr. Steinman's] report show an expect value that indicates there is nothing particularly notable about the homology he found." Tr. 217:18–23. In a BLAST search tutorial, Wheeler and Bhagwat[53] explained that "[t]he '[e]xpect [v]alue' is the number of times that an alignment as good or better

[52] Daniel Weibel et al., *Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines – Multi-Country assessment*, 36 VACCINE 6202 (2018).

[53] David Wheeler & Medha Bhagwat, Blast QuickStart. In: Bergman NH, editor. Comparative Genomics: volume 1 and 2. Totowa (NJ): Humana Press; 2007.

than that found by BLAST would be expected to occur by chance . . . . A higher '[e]xpect [v]alue' threshold is less stringent and the BLAST default of '10' is designed to ensure that no biologically significant alignment is missed." Resp't's Ex. V at 3 (quoting Resp't's Ex. W at 2, ECF No. 70-2). Wheeler and Bhagwhat noted that "'[e]xpect [v]alues' in the range of 0.001 to 0.0000001 are commonly used to restrict the alignments shown to those of high quality." Resp't's Ex. W at 2. Dr. MacGinnitie noted that Dr. Steinman's BLAST search result had an expect value of 5.3, which is "well above the range accepted to be significant[.]" Resp't's Ex. V at 3.

Although Dr. MacGinnitie stated that evidence of a "T cell response against hypocretin in patients with narcolepsy would be sort of strong evidence for" and "provide the mechanism" of autoimmunity, Dr. MacGinnitie stated that the Latorre article "makes pretty clear that they did not see any cross-reactivity between the hypocretin-specific T cells they saw in influenza." Tr. 218:11–14. He acknowledged, however, that he does not know if there was nucleoprotein in what the authors tested. Tr. 218:15–17. Dr. MacGinnitie noted that the Latorre study concerned a limited number of patients. Tr. 219:15–16. He remarked that "[t]he T cells are what we call restricted by HLA types and the restriction they found was not to the DQ, but DR, which is not entirely clear why that would be[] . . . ." Tr. 219:16–19. In his first expert report, Dr. MacGinnitie explained that "HLA protein presents peptides (protein fragments) on the surface of cells. The HLA-peptide combination is recognized by T[] cells which, when activated, can both kill infected cells and provide help to B cells to generate antibodies." Resp't's Ex. A at 4. He continued that "[c]rucially, the linkage to a specific HLA allele indicates the obligate involvement of T[] cells which recognize this HLA type in the pathogenesis of disease." *Id.* Regarding that Latorre found T cells restricted to DR, rather than DQ, HLA types, Dr. MacGinnitie stated that he "think[s] that this [is] because this study found . . . these T cells and then incubated them with influenza antigens, it did not see that the T cells were activated by influenza antigens[.]" Tr. 219:19–23. He averred that this detracts from the notion that there is "molecular mimicry between influenza in general and narcolepsy." Tr. 219:23–24. Furthermore, Dr. MacGinnitie noted that, of the nineteen patients studied in the Latorre article, only three had type 2 narcolepsy. Resp't's Ex. S at 3. He stated that "reactive T-cells were found in [three] of [twelve] controls who do not have narcolepsy." *Id.* He also noted that the authors "only consistently identified hypocretin T-cells using one of" the two methods they used to look for them. *Id.* He also stated that the authors did not indicate that the T cells they found were pathological. Resp't's Ex. S at 4.

Dr. MacGinnitie rejected Dr. Steinman's reliance on the Gautam articles because "they had to use [C]omplete Freund's [A]djuvant [("CFA")],[54] which is a very powerful immune stimulant, such that it[is] not even widely used in animals because of the inflammation it triggers." Tr. 224:19–225:10. Dr. MacGinnitie also noted that these articles are about thirty years old and did not involve narcolepsy. Resp't's Ex. S at 7. He concluded that "the mouse model on which Dr. Steinman's theory of causation is based is very different from that of Flu[M]ist vaccination, has no relevance to human narcolepsy, and is of, at best, questionable significance." Resp't's Ex. S at

[54] Freund adjuvant is "a water-in-oil emulsion incorporating antigen, in the aqueous phase, into lightweight parrafin oil with he aid of an emulsifying agent[, which] induces strong persistent antibody formation." Complete Freund's Adjuvant is formed with "[t]he addition of killed, dried mycobacteria[] . . . to the oil phase" and "elicits cell-mediated immunity (delayed hypersensitivity), as well as humoral antibody formation." *Freund Adjuvant*, DORLAND'S, https://www.dorlandsonline.com (last visited Apr. 29, 2022).

7. Dr. MacGinnitie also stated that "Root-Bernstein says you need adjuvants to see autoimmunity and molecular mimicry in animals[.]" Tr. 225:11–12.

Dr. MacGinnitie further opined that Dr. Steinman "downplayed the extent to which there[is] significant homology among all viruses, bacteria, and human protein[]" and thinks that the Kanduc[55] and Trost[56] articles he filed provide evidence that the five out of ten match "is not significant clinically." Tr. 223:16–22. Dr. MacGinnitie also denied that the Root-Bernstein article is significant in this case because the five-out-of-ten amino acid similarity was "just the filter that somebody chose to do their searches." Tr. 223:23–224:7.

He noted that Kanduc et al. "determined that each viral genome (of [thirty] studied) had multiple instances of [five], [six], and even [seven] amino acid peptides identical to human peptides (and that is 100% identical of a consecutive stretch of amino acid.)" Resp't's Ex. S at 7–8 (citing Resp't's Ex. S, Tab 10, ECF No. 63-1). The authors concluded that "the massive viral to human peptide overlapping calls into question the possibility of a direct causal association between virus-host sharing of amino acid sequences and incitement to autoimmune reactions through molecular recognition of common motifs." Resp't's Ex. S, Tab 10 at 1. Dr. MacGinnitite also cited the Trost article, which showed, in a study of forty bacterial species, that "all bacterial proteomes . . . share hundreds of nonamer sequences with the human proteasome." Resp't's Ex. S at 8 (quoting Resp't's Ex. S, Tab 11 at 2, ECF No. 63-2). Dr. MacGinnitie asserted that these articles "demonstrate the limited sequence identified by Dr. Steinman . . . obtained using the BLAST tool is not of clinical significance." Resp't's Ex. S at 8. Dr. MacGinnitie further opined that "[s]equence similarity is not enough to trigger autoimmunity." Resp't's Ex. V at 2.

Dr. MacGinnitie noted that he performed his own BLAST search of the "GTEFKPRSAL peptide versus the entire human genome[]" and stated that "the results show that the cross-reactivity with hypocretin/orexin is unremarkable." *Id.* at 4. As addressed by Dr. Steinman, Dr. MacGinnitie noted that "[t]here were several more similar matches including a [six of seven] match with a zinc-finger protein and a [six of six] match with the immunoglobulin gamma-chain in addition to a number of other exact [five of five] matches . . . ." *Id.* He noted that when he searched the whole human genome rather than just comparing it to the orexin peptide, "orexin/hypocretin was not identified at all[.]" *Id.* Dr. MacGinnitie explained that his "search was to look for all the human proteins that cross-reacted with the nucleoprotein, and what [he] found was that there was not significant or notable homology with the hypocretin." Tr. 216:23–217:2. Dr. MacGinnitie noted, however, that Dr. Steinman's "starting point was looking for this very specific homology between hypocretin and nucleoprotein B[] . . . ." Tr. 215:25–216:3.

Dr. MacGinnitie explained that his understanding of the IEDB is that "it[is] just a database where any number of possible epitopes for an immune response have been deposited." Tr. 220:3–7. He disagreed with Dr. Steinman that the IEDB supports Petitioners' theory. Dr. MacGinnitie explained that "the sequence that was fed in was actually the peptide from nucleoprotein B, and then what was identified is another similar peptide from another strain of influenza." Tr. 220:8–

[55] Darja Kanduck et al., *Massive peptide sharing between viral and human proteomes*, 29 PEPTIDES 1755 (2008).
[56] Brett Trost et al., *Bacterial peptides are intensely present throughout the human proteome*, 1(1) SELF/NONSELF 71 (2010).

15. Dr. MacGinnitie did not "think it[is] any support for the theory that there[is] cross-reactivity between two different influenza strains." Tr. 220:15–18. Dr. MacGinnitie thought that it would be significant if the input was a sequence from hypocretin and if it showed cross-reactivity with something in influenza. Tr. 220:19–23. However, he maintained that "it[is] no surprise that there[is] similarity between two different nucleoproteins from two different type B influenza strains." Tr. 220:24–221:1.

During cross-examination, Dr. MacGinnitie was asked to discuss the scientific community's view on molecular mimicry as a mechanism underlying autoimmune disease. Tr. 238:3–6. Dr. MacGinnitie stated that he "think[s] that it[is] seen as a strong hypothesis, and in certain illnesses, like rheumatic fever, it[is] considered . . . by far the most likely hypothesis." Tr. 238:7–10. Citing Root-Bernstein, however, Dr. MacGinnitie stated that "there[is] really not such strong evidence in humans for [molecular mimicry] as a general mechanism for autoimmune disease." Tr. 238:10–15. On redirect, Dr. MacGinnitie opined that mimicry alone is not enough to cause autoimmune disease. Tr. 254:10–11. He indicated that the IOM report[57] Respondent submitted showed an antibody response to tissues without clinical disease. Tr. 254:22–255:2 (citing Resp't's Ex. R, ECF No. 51-6) Dr. MacGinnitie stated that the Ahmed study, in which not every patient with the antibodies had the disease, was an example of this. *See* Tr. 255:2–6.

I asked Dr. MacGinnitie about a differentiation he had made earlier between markers of immune damage and causes of immune damage. Tr. 242:22–24. Dr. MacGinnitie maintained that the difference can be evaluated in some circumstances, such as in type 1 diabetes in which gradual changes in antibody levels are observable, but not in others. He stated that the Ahmed study did not present evidence that the antibodies were pathogenic. Tr. 243:1–18.

Given Dr. MacGinnitie's statements indicating that cross-reactivity should result in cross-reaction everywhere in the body where such a reaction could occur, I asked Dr. MacGinnitie to account for examples of targeted autoimmune diseases. Tr. 243:19–244:10. Dr. MacGinnitie explained that "different tissues express different proteins[]" and that some proteins only target specific areas. Tr. 244:11–18. However, the hypocretin receptor in focus in the Ahmed study "is expressed widely throughout the central nervous system." Tr. 244:19–21. Thus, "if we saw an immune attack against that receptor, we would expect not just narcolepsy, but other neurologic issues." Tr. 244:19–23. He explained that "[t]he Latorre study, which really looks at T cells just against neurons that secrete hypocretin, intuitively makes more sense, because the immune response is against the cells that are lacking in the disease." Tr. 244:25–245:4.

Dr. MacGinnitie denied that molecular mimicry is always pathogenic. Tr. 245:5–7. Without conceding that the antibodies in the Ahmed study were generated by molecular mimicry, but accepting it for the sake of argument, Dr. MacGinnitie noted that some patients had the antibodies but did not have narcolepsy. Tr. 245:8–17.

Dr. MacGinnitie stated that "only adjuvanted H1N1 vaccine has been epidemiologically linked to the development of narcolepsy." Tr. 198:6–7. Noting that not all adjuvanted H1N1 vaccines were epidemiologically linked to narcolepsy, Dr. MacGinnitie opined that "it looks like

[57] Institute of Medicine Adverse Effects of Vaccines: Evidence and Causality 70–73, 314–21 (Kathleen Stratton et al. eds. 2012).

receipt of an adjuvanted vaccine was necessary to see the signal of increased narcolepsy, but not sufficient." Tr. 198:8–13. Dr. MacGinnitie noted that Dr. Steinman relied on studies involving adjuvants and stated that "in these animal models . . . you need to use often a powerful adjuvant to see any evidence of autoimmunity, that the exposure to the antigen itself[] . . . is not enough." Tr. 199:4–9.

In his second expert report, Dr. MacGinnitie addressed the SOMNIA study. Dr. MacGinnitie stated that "there is actually no relationship between adjuvanted [flu] vaccination and narcolepsy. Rather, several cases were, by chance, identified after vaccination and the resulting publicity and awareness among both the public and physicians led to cases being diagnosed sooner and, probably, to increased attention being paid to patients with complaints of fatigue and increased somnolence that occurred after vaccination." Resp't's Ex. S at 1–2. He explained that the SOMNIA study "was [] undertaken to better understand the relationship between adjuvanted [flu] vaccination and narcolepsy[]" and that "[t]he study clearly found that narcolepsy rates were only increased in Sweden and Taiwan." *Id.* at 2 (citing Resp't's Ex. S, Tab 2 at 2). He noted that the increase in Sweden was observed when wild-type H1N1 was circulating and when, simultaneously, Pandemrix was being administered. *Id.* (citing Resp't's Ex. S, Tab 2 at 8). He noted that H1N1 was circulating in Taiwan during the time of the study without widespread vaccination. *Id.* (citing Resp't's Ex. S, Tab 2 at 2). However, in his initial report, Dr. MacGinnitie acknowledged a "clear . . . association between the Pandemrix vaccine and new-onset narcolepsy." Resp't's Ex. A at 6.

Addressing the differences between Pandemrix and FluMist, Dr. MacGinnitie explained that "[s]ubunit vaccines are produced by growing [three] or [four] different [flu] strains on chicken oocytes and then inactivating the viruses using formaldehyde or beta-propiolactone . . . ." Resp't's Ex. A at 10. Dr. MacGinnitie noted that these vaccines are administered intramuscularly or under the skin after purification of the protein components and that some formulations include adjuvants to increase the immune response. *Id.* at 10–11. He noted that LAIVs, "while also grown on egg cells, are selected so they can only grow effectively at lower temperatures . . . . The viruses are delivered into the nose where they are able to replicate in the nasal epithelium." *Id.* at 11. Dr. MacGinnitie explained that "[t]he temperature sensitivity of these attenuated viruses prevents replication in the lungs, preventing severe vaccine associated illness." *Id.* Dr. MacGinnitie noted that these different types of vaccines, while both effective at preventing flu, cause different immune responses. *Id.* Dr. MacGinnitie stated that Pandemrix was an adjuvanted subunit vaccine. *Id.* Citing a paper by Waddington et al.,[58] Dr. MacGinnitie stated that "[d]ata show that by some parameters (antibody titers against hemagglutinin) [] Pandemrix [] elicited a response 3.5 to [ten] times greater than non-adjuvanted vaccine." *Id.* (citing Resp't's Ex. A, Tab 16 at 5, ECF No. 48-7). He noted that FluMist is a LAIV and that all flu vaccines administered in the United States are non-adjuvanted. *Id.* Dr. MacGinnitie stated that "narcolepsy has only been associated with certain adjuvanted subunit [flu] vaccines[,]" including the vaccine studied by Montplaisir et al. in Canada. *Id.* at 12 (citing Pet'r's Ex. 61).

[58] Claire S. Waddington et al., *Safety and immunogenicity of AS03$_B$ adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomized, parallel group, multicentre study*, 340:c2649 BMJ 1 (2010).

Dr. MacGinnitie maintained that there is no data linking FluMist to narcolepsy. *Id.* at 6–7. When asked about the Duffy study, Dr. MacGinnitie opined that "it[is] an excellent study and provides very strong evidence against FluMist being a trigger of type 1 narcolepsy." Tr. 199:22–24. Addressing Dr. Steinman's criticisms of the Duffy article, Dr. MacGinnitie stated that "Duffy identified zero cases of narcolepsy in 340,000 receiving [LAIV] in 2009 and 2010 making any suggestion that this study was not large enough to find an increased risk implausible." Resp't's Ex. V at 1. Dr. MacGinnitie noted that CDC-sponsored research into the rates of narcolepsy following H1N1 vaccination and wild infection varied depending on the country regarding the association with vaccination and infection. Tr. 202:21–203:9. Dr. MacGinnitie stated that the takeaway to him was that "the only association seen with H1N1 vaccination in narcolepsy was with adjuvanted vaccine and in Nordic" or northern European countries. Tr. 203:10–14. Dr. MacGinnitie noted that narcolepsy was associated with H1N1 infection in Taiwan only and stated that this "is hard to explain in any simple way[.]" Tr. 203:14–17. Citing the increase in Scandinavia, he noted the possibility of an association between wild-type H1N1 infection and narcolepsy and suggested the possibility that wild-type H1N1 infection and vaccination occurring in close proximity may trigger narcolepsy. Resp't's Ex. S at 3. Dr. MacGinnitie also addressed the Han study, which showed apparent seasonal presentation of narcolepsy in China and an increase in narcolepsy after H1N1 circulated. Tr. 203–204 (citing Pet'r's Ex. 64 at 1). Dr. MacGinnitie, however, did not think that this study supported causation. *See* Tr. 204. He quoted an article by Julkunen,[59] in which the authors stated that "it must be pointed out that seasonal [flu] vaccines, which are given yearly to hundreds of millions of people, have not been associated with narcolepsy." Resp't's Ex. A at 12 (quoting Resp't's Ex. A, Tab 19 at 2, ECF No. 48-10).

Addressing Dr. Steinman's comment that the HLA-DQB1*0602 genetic variant is less common in the United States than other parts of the world, Dr. MacGinnitie stated that the rate of this variant is two to three times higher in Scandinavia than the United States. Resp't's Ex. S at 6. However, noting that the population of the United States is more than twenty times that of Sweden and Finland combined, Dr. MacGinnitie averred that a link between the flu vaccine and narcolepsy, if present, should be evident in studies such as the Duffy study. *Id.* at 6–7.

Petitioners' counsel asked Dr. MacGinnitie if the Duffy and SOMNIA studies "taken together prove that a live virus flu vaccine cannot cause narcolepsy." Tr. 28:19–22. Dr. MacGinnitie said no and stated that he "think[s] Duffy shows[that FluMist] did not result in an increase in narcolepsy in the United States in the year studied." Tr. 228:23–229:1. He noted that the SOMNIA study involved subunit vaccines rather than live virus vaccines. Tr. 229:5–18. He again indicated that "the take-home message is that it was only adjuvanted vaccines and only in a specific – in this study, in one country that [narcolepsy] increased after vaccination." Tr. 229:20–23. Dr. MacGinnitie acknowledged that the Duffy and SOMNIA studies were not able to identify whether people diagnosed with narcolepsy were previously exposed to the flu virus. Tr. 232:9–14.

When asked if he would distinguish between an adjuvanted vaccine's ability to cause autoimmune disease through molecular mimicry and an unadjuvanted live virus vaccine's ability, Dr. MacGinnitie answered affirmatively "[i]n this case[.]" Tr. 238:15–19. He continued that he believes "it[is] clear in this case that adjuvanted H1N1 vaccine . . . apparently triggered increased

[59] Ilkka Julkunen & Markku Partinen, *Disease mechanisms in narcolepsy remain elusive*, 10 NAT. REV. NEUROl. 616 (2014).

risk of narcolepsy." Tr. 238:19–21. He also stated that "in general if we accepted that an infection can cause it, then a live attenuated vaccine could also potentially trigger it. [His] objections are specific to this case, not to the general idea." Tr. 238:21–25.

During my questioning, Dr. MacGinnitie stated that he "think[s] there is a big difference in the immune response to an injected antigen versus the live attenuated virus[.]" Tr. 246:18–20. Noting that the FluMist is sprayed up the nose and "infects the cells in [the] upper airway and generates a much less strong immune response than . . . subunit vaccines, at least throughout the body[,]" Dr. MacGinnitie remarked that FluMist "sort of replicates or imitates a natural infection[. I]t generates a stronger immune response in [the] sinuses and lungs and upper airway, and so [there is] less overall response [] throughout [the] body, but a stronger response where" needed. Tr. 246:20–247:5.

I also asked Dr. MacGinnitie to explain how the differences between influenza strains impact this case. Tr. 248:17–23. Dr. MacGinnitie averred that "the whole narcolepsy/influenza connection is really based on H1N1," an influenza A strain. Tr. 248:24–249:1. Discussing Dr. Steinman's theory, Dr. MacGinnitie stated that he "assume[s] if there was a relation with the A strain, we would have heard about it, because that would have been a much stronger theory . . . ." Tr. 249:9–11.

Dr. MacGinnitie agreed with Petitioner's counsel that it is possible that molecular mimicry was the mechanism underlying increases in narcolepsy attributed to Pandemrix, but Dr. MacGinnitie maintained that "we do[not] know yet[.]" He continued that, in light of the medical literature, "it[is] most likely, but not yet demonstrated." Tr. 239:1–16.

Petitioner's counsel asked Dr. MacGinnitie whether he agreed that epidemiology is more useful for assessing population-level vaccine safety than assessing whether a vaccine can injure an individual. Tr. 232:15–19. Dr. MacGinnitie agreed, stating that "it[is] impossible to prove a negative." Tr. 232:20–21. Dr. MacGinnitie maintained, however, that epidemiology can be helpful in a case even though it is "less powerful at an individual level than at a population level." Tr. 232:22–24. Dr. MacGinnitie also acknowledged that there is some evidence that influenza infection could cause narcolepsy in some cases, but he characterized this evidence as suggestive rather than conclusive. Tr. 232:25–233:4.

Petitioner's counsel asked Dr. MacGinnitie about the abstract discussed by Dr. Steinman. Tr. 233:5–12. Describing his own experience peer-reviewing abstracts, Dr. MacGinnitie explained that he, at an annual meeting, will review about sixty abstracts in an hour and a half and that he does not have access to the data the abstract is based on. Tr. 233:18–23. Dr. MacGinnitie noted that when reviewing a paper, he will spend two to three hours carefully evaluating it. Tr. 233:24–234:2. He also stated that the abstract in question "suffers from the same problems that Han does[. It is] just a report from a number of centers in the U.S. saying[that they are] seeing more narcolepsy[] . . . at the same time as H1N1[] . . . ." Tr. 234:4–11. Dr. MacGinnitie stated that the abstract suggests that wild H1N1 could trigger narcolepsy but opined that it is not strong evidence. Tr. 234:12–14.

I asked Dr. MacGinnitie if the increase in immune activity following an adjuvanted vaccine is because an adjuvant "by definition increase[s] the change of autoimmunity[]" or if "there [is] something specific about adjuvants that increases [the] likelihood of autoimmunity[.]" Tr. 240:14–21. Dr. MacGinnitie stated that this is "an active area of research[]" and that he thinks "it[is] a little bit of both[.]" Tr. 240:22–25. He opined that "the stronger an immune response you generate to a specific protein, the more chance that, [] if that protein . . . has homology, that molecular mimicry will occur[]" but that "part of the way that adjuvants work is by just stimulating general inflammation[.]" Tr. 241:1–6. Dr. MacGinnitie continued that "it[is] difficult to use [CFA], even in animals[]" and that it is not used in humans "because it caused such painful local swelling. And we think that inflammation is one of the things that can also sort of break tolerance or lead to autoimmunity. So [he] think[s] it could be either or a combination." Tr. 241:7–13.

I noted that "clearly there were enough people that thought there was a connection here where you have the amount of money and effort and research that it took to produce something like Duffy." Tr. 241:22–25. Noting that "we[are] already talking about something that is such a rare event," I asked Dr. MacGinnitie, "if there was smoke, . . . is there not fire?" Tr. 242:1–7. Dr. MacGinnitie stated that he "think[s] that yes, there[is] fire in the case of adjuvanted vaccines, at least in specific countries," but that he thinks "because there was a fire one place, people started looking for fires other places, and they did[not] find it." Tr. 242:15–18.

On cross-examination, Dr. MacGinnitie stated that, because only a small fraction of individuals carrying the genetic component develop narcolepsy, he "think[s] the natural idea is to figure there must be some environmental trigger." Tr. 227:11–17. He opined that "until such triggers are identified, it[is] also possible that it[is] random somehow[.]" Tr. 227:17–19. However, he maintained the notion of environmental influence is reasonable. Tr. 227:19–20. Dr. MacGinnitie noted that, in general, infections are "often felt to be a trigger for autoimmun[e] disease[]" and that "at least in some populations in some circumstances, adjuvanted subunit vaccines can trigger [autoimmune disease]." Tr. 228:1–8. He did not think sufficient epidemiological data exists to support that the flu virus can trigger autoimmune disease. Tr. 228:9–18.

Dr. MacGinnitie acknowledged that type 1 narcolepsy is generally marked by the lack of hypocretin in cerebrospinal fluid. Tr. 221:2–6. However, Dr. MacGinnitie did not know how long it takes to reduce the hypocretin to the point that symptoms of narcolepsy present. Tr. 221:7–14. When asked, he thought that it might take longer than one to two months to observe the clinical result of hypocretin depletion. Tr. 221:18–22. He noted that "the Duffy study used six months as the onset of symptoms that would be reasonable within six months [sic], although they also looked at a year and did[not] see anything." Tr. 221:18–25. However, Dr. MacGinnitie stated that this is "not well studied[]" and noted that, because narcolepsy is generally not diagnosed early in its progression, he does not know if there have been "a lot of patients who are [] caught early and then their progression can be measured." Tr. 222:1–7. Regarding temporal association in this case, Dr. MacGinnitie opined that "whether it[is] four to eight weeks or four months in this case, . . . that[is] not strong evidence one way or the other." Tr. 222:8–14.

Petitioners' counsel also asked Dr. MacGinnitie if he believes it is "scientifically practical to provide direct proof that molecular mimicry has occurred in a specific individual who has

autoimmune disease." Tr. 239:17–20. Dr. MacGinnitie acknowledged that this "would be very difficult[]" in a vaccine hearing. Tr. 239:17–22. Dr. MacGinnitie stated that evidence of "a tissue-specific response" in an individual would provide some evidence of causation but that "[t]here[is] no evidence of autoimmunity specific to this case." Tr. 254:15–21.

I asked Dr. MacGinnitie to explain how to identify narcolepsy onset when a patient might experience vague tiredness not yet attributable to narcolepsy leading up to an eventual narcolepsy diagnosis. Tr. 249:13–250:12. Dr. MacGinnitie stated that he would refer to the neurologist on whether narcolepsy is progressive but that he believed that narcolepsy could appear progressive as a patient's hypocretin diminishes. Tr. 251:6–20.

Dr. MacGinnitie also stated that he disagreed with Dr. Steinman that V.H. experienced a recall response. Tr. 251:21–23. Dr. MacGinnitie asserted that people get flu vaccinations yearly because the strains change, not because the initial immune response was deficient. Tr. 251:23–25. He continued that the first FluMist vaccine V.H. received would have contained different strains than the FluMist vaccine V.H. received in 2012. Tr. 252:5–8. He also mentioned that associations between H1N1 and narcolepsy occurred when patients were first exposed to H1N1, and "[t]hat[is] the reason there was a pandemic." Tr. 252:8–11.

3. Respondent's Expert, Dr. Raizen

Dr. Raizen filed two expert reports and testified at the hearing. *See* Resp't's Ex. C; Resp't's Ex. T, ECF No. 64-1; Tr. 164–193. Dr. Raizen explained the process he uses to diagnose patients with narcolepsy. Tr. 167–168. He stated that the difference between narcolepsy types 1 and 2 is that type 1 is associated with narcolepsy while type 2 is not. Tr. 168:18–22. He explained that "[t]ype 1 [n]arcolepsy is characterized by excessive daytime sleepiness, paralysis on transitions between sleep and wake, hallucination on sleep/wake transitions, cataplexy, and sleep fragmentation." Resp't's Ex. C at 3. He noted that approximately one in 2000 people experience type 1 narcolepsy and that "[s]ymptoms usually begin in the second or third decade of life." *Id.* Dr. Raizen stated that "[t]here is no question in [his] mind[]" that V.H. has type 1 narcolepsy. Tr. 168:24–169:3.

Dr. Raizen emphasized that "[l]oss of hypocretin neurons is a core component of the pathophysiology of narcolepsy[.]" Resp't's Ex. C at 3. He explained that "[t]here are two highly similar hypocretin peptides in the human brain: Hypocretin 1 (also known as orexin-A) is made up of [thirty-three] amino acids, and hypocretin 2 (also known as orexin-B) is composed of [twenty-eight] amino acids." *Id.* at 4. He explained that "[h]ypocretin 1 and 2 are synthesized as part of a single protein, called preprohypocretin, which is processed into the hypocretin 1 and hypocretin 2 peptides." *Id.* Dr. Raizen noted that "[t]he preprohypocretin protein is found only in the small number of neurons deep in the brain in region [sic] called the posterior lateral hypothalamus." *Id.* He explained that "[a]lthough preprohypocretin is made in just a small number of deep brain neurons, these neurons project to many brain regions, where they release the hypocretin 1 and 2 peptides. These peptides then act on hypocretin receptors 1 and 2, which are widely expressed." *Id.* Dr. Raizen noted that the "understanding of the pathophysiology of narcolepsy[]" has relied on studies on rodents and dogs, which "have shown that a syndrome very similar to human narcolepsy can develop with removal of either the gene encoding

preprohypocretin or by the removal of the hypocretin receptor 2." *Id.* However, he maintained that studies of narcolepsy patients show that the loss of neurons forming preprohypocretin, rather than loss of the receptors, results in human narcolepsy. *Id.* He stated that "[t]his conclusion is based on the observation of low concentrations of hypocretin peptides in the cerebrospinal fluid obtained from narcoleptic patients and an absence of hypocretin neurons in the brains (analyzed post-mortem) of narcoleptic individuals." *Id.* In his first expert report, Dr. Raizen criticized Dr. Steinman's first theory, in part, because it "does not connect to a key pathophysiologic pillar of type 1 narcolepsy pathogenesis, the destruction of hypocretin neurons." *Id.* at 6. He questioned why "other neurons expressing the hypocretin receptor two [are] spared in this disease[.]" *Id.*

Dr. Raizen also agreed with Dr. Steinman that almost everyone with type 1 narcolepsy has HLA-DQB1*0602, stating that more than ninety-eight percent of narcoleptics have this genetic variant. Tr. 169:8–15. Dr. Raizen agreed that the genetic variant is not by itself sufficient to indicate that someone will develop narcolepsy. Tr. 169:14–15. He explained that the HLA type indicates susceptibility but that "something else must happen for the disease to develop. What that something else is is not understood." Tr. 169:22–170:1. Dr. Raizen agreed that "the evidence supports that [narcolepsy is] an autoimmune disease[ ] in most cases." Tr. 170:25–171:4. He explained that "[t]he strong association between narcolepsy and a particular HLA antigen, as well as an association with genetic variants of the T cell receptor, which are both parts of the immune system[]" gave rise to the hypothesis that narcolepsy is an autoimmune condition. Resp't's Ex. C at 4. Dr. Raizen noted that "observation of increased antibody titers against upper respiratory pathogens in narcoleptics in comparison to non-narcoleptics[]" supports that type 1 narcolepsy has an immune etiology. *Id.* While he noted that there is no empiric evidence demonstrating a relationship between FluMist and type 1 narcolepsy, Dr. Raizen stated that the increase of narcolepsy in China following the H1N1 pandemic and the increase in Europe following Pandemrix support an immune etiology. Resp't's Ex. C at 4–5. He also noted that the Latorre article "supports a cellular autoimmune mechanism directed against the hypocretin protein." Resp't's Ex. T at 1. He stated that type 1 narcolepsy is not associated with other autoimmune diseases. Tr. 171:7–8.

Dr. Raizen explained that, based on his knowledge and experience as a clinician, narcolepsy "is not associated with a prodrome." Tr. 170:10–12. He stated that "there[is] often a long lag between symptom onset and diagnosis, perhaps because it[is] underappreciated, but there is typically no clear prodrome of a fever or an infectious illness." Tr. 170:13–16. Dr. Raizen noted that many of his patients, when trying to identify a cause of their narcolepsy, ask him about the relationship between narcolepsy and the flu vaccine. Tr. 170:17–21. He indicated that he recommends the flu vaccine to his narcoleptic patients. Tr. 170:22–24.

Dr. Raizen was asked if there are signs of inflammation in narcoleptics. Tr. 171:14–15. Dr. Raizen stated that this issue has been examined in a few ways, including with MRI. Tr. 171:18–19. He continued that "[t]here is a technique called contrast-enhanced MRI that can detect evidence of inflammation in the brain, or at least consequences of inflammation in the brain, or at least consequences of inflammation, and those studies have not revealed any abnormalities to suggest inflammation." Tr. 171:20–24. Dr. Raizen noted that researchers have looked for inflammation during autopsy studies of patients with narcolepsy. Tr. 172:6–9. He stated that these "papers did not find any evidence of inflammation in the brain anywhere, particularly not in the hypothalamus

where the hypocretin neurons are located." Tr. 172:10–13. When asked if immune-modifying medications, such as steroids or IVIG, had been found to help patients with narcolepsy, Dr. Raizen stated that in the limited number of times this has been attempted, these treatments appeared unsuccessful. Tr. 172:14–21. Because type 1 narcolepsy presents differently than other autoimmune conditions, Respondent's counsel asked Dr. Raizen if it is "fair to extrapolate what we know about other autoimmune conditions and apply it to narcolepsy[.]" Tr. 173:4–8. Dr. Raizen responded that he does not think this would be "entirely fair, just because of the difficulty in assessing the part of the brain that needs to be assessed." Tr. 173:9–12. He explained that "[f]or example, [in] rheumatoid arthritis[,] . . . it[is] easy to assess the joints because they[are] peripheral, but it[is] not so easy to assess deep in the brain." Tr. 173:12–15.

Dr. Raizen was asked if the medical community, and specifically the community of neurologists specializing in sleep medicine, believes that the flu vaccines used in the United States more likely than not cause narcolepsy. Tr. 177:1–6. Dr. Raizen said no and stated that "there[has] never been any evidence to support that." Tr. 177:7–8.

Dr. Raizen indicated that he does not find Dr. Steinman's theory regarding components of influenza B compelling. Tr. 177:15–21. Dr. Raizen stated that he "searched the literature as best as [he] could, [and he] could not find any papers showing an association between an immune response to influenza B and incident narcolepsy, nor did [he] find anyone proposing that influenza B is involved in the pathogenesis of narcolepsy." Tr. 178:8–13. Dr. Raizen stated that "there was no evidence of an immune response, either antibody or T cell associated with influenza B that was . . . associated with narcolepsy." Tr. 178:24–179:2. Dr. Raizen rejected Dr. Steinman's assertion that a spike in influenza B may have explained the increase in narcolepsy seen in the Han study. Resp't's Ex. T at 2. Dr. Raizen noted that Han et al. did not mention influenza B. *Id.* He also noted that the Pandemrix vaccine "did not contain influenza B antigens." *Id.* He stated that "there has never been a report of enrichment for antibodies or T cell reactivity toward influenza B antigens in narcoleptics." *Id.*

Dr. Raizen discussed the epidemiological studies in the record, including Duffy and the Weibel et al. study, which he stated "examined the risk of narcolepsy after exposure to adjuvanted influenza A vaccines in seven countries." Resp't's Ex. T at 3. Dr. Raizen averred that the Weibel study "suggests that there was something special about the Finish [sic] and Swedish 2009/2010 narcolepsy cluster." *Id.* Dr. Raizen concluded that "[t]aken together, the Duffy and Weibel studies show that, unless living in Finland or Sweden in 2009/2010 and receiving the Pandemrix vaccine, an individual receiving an influenza vaccine has no greater risk for narcolepsy than an individual not receiving this vaccine." *Id.*

On cross-examination, Dr. Raizen was asked about the significance of inflammation not being found in narcolepsy patients. Tr. 180:7–9. Dr. Raizen stated that there were a couple of ways to look at this. Tr. 180:10–11. Dr. Raizen noted that this may mean that there is no inflammation in narcolepsy, which would suggest it is not an autoimmune disease. Tr. 180:11–14. However, he noted that "there is [sic] limitations to . . . how well we can probe for inflammation, and the [MRI] study, while very powerful and used to assess inflammation for certain neurological diseases, may not be sensitive enough to pick up inflammation in the small part of the brain called the hypothalamus." Tr. 180:15–20. Dr. Raizen also stated that the absence of inflammation at the time

of an autopsy "perhaps years after the onset of inflammation[]" may not indicate that inflammation was absent earlier. Tr. 180:21–181:2.

I asked Dr. Raizen to elaborate more on the relationship between narcolepsy's genetic component and a potential trigger. *See* Tr. 186. Dr. Raizen stated that "an environmental trigger can be many things[,]" including an infection, vaccine, or chemical. Tr. 187:5–9. He indicated that "the easiest trigger to think about is something that affects the immune response in some fashion or another[,]" such as an infection. Tr. 188:17–20. Dr. Raizen also addressed the possibility of a nonautoimmune response, citing an article by Goel et al.[60] which demonstrated that people with the HLA-DQB1*0602 variant who did not have narcolepsy "were more likely to be sleepy than people who did not have the [HLA-DQB1*0602] variant." Tr. 189–190:2. Dr. Raizen explained that if HLA-DQB1*0602 has another function besides an immune function "such as in the manifestation of sleepiness, that could explain the association with the disease and not involve an autoimmune process." Tr. 191:2–9. Dr. Raizen also stated that "it[is] very likely that there are multiple genes that predispose to type 1 narcolepsy." Tr. 191:17–19.

IV. Applicable Legal Standards

To receive compensation under the Vaccine Act, a petitioner must demonstrate either that: (1) the petitioner suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as modified by 42 C.F.R. § 100.3; or (2) that petitioner suffered an "off-Table injury," one not listed on the Table, as a result of his receiving a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioners do not allege a Table injury in this case; thus, they must prove that V.H.'s injury was caused-in-fact by a Table vaccine.

To establish causation-in-fact, a petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). A petitioner is required to prove that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321–22 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Sec'y of the Dept. of Health & Hum. Servs*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278–79 (Fed. Cir. 2005). The *Althen* test requires petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.* "[C]lose calls regarding causation are resolved in favor of injured claimants." *Id.* at

[60] Namni Goel et al., *DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue*, 75 NEUROLOGY 1509 (2010).

1280. Further, evidence used to satisfy one prong of the test may overlap to satisfy another prong. *Capizzano*, 440 F.3d at 1326.

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Hum. Servs*., 98 Fed. Cl. 719, 726 (2011). A petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994). In such a case, the government must not merely prove the existence of an alternative cause, but that such an alternative actually caused the injury. *Knudsen*, 35 F.3d at 549. Consequently, when and if the petitioner establishes a prima facie case, the burden then shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *See de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1354 (Fed. Cir. 2008); *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that the respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe v. Sec'y of Health & Hum. Servs.*, 601 F.3d 1349 (Fed. Cir. 2010) (stating that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

V. Discussion

A. *Althen* Prong One

Under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question: "can the vaccine[] at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Hum. Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *mot. for rev. denied*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548–49. Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge[] the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). Scientific and "objective confirmation" of the medical theory with additional medical documentation is unnecessary. *Althen*, 418 F.3d at 1278–81; *see also Moberly*, 592 F.3d at 1322. However, as the Federal Circuit has made clear, "simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) (citing *Moberly*, 592 F.3d at 1322). Indeed, the Federal Circuit has "consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, (Fed. Cir. 2019) (citing *Moberly*, 592 F.3d at 1322 and *LaLonde*, 746 F.3d at 1339). Rather, "[a] petitioner must provide a reputable medical or scientific explanation that pertains specifically to

the petitioner's case." *Moberly*, 592 F.3d at 1322. In general, "the statutory standard of preponderance of the evidence requires a petitioner to demonstrate that the vaccine more likely than not caused the condition alleged." *LaLonde,* 746 F.3d at 1339.

Furthermore, establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of her claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357,1361(Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. However, in the Vaccine Program, the *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (2010) ("[U]niquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted."); *see also Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). Under *Daubert*, the

> factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors are "meant to be helpful, not definitive." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151 (1999). The factors do not "constitute 'a definitive checklist or test'" and may be applied differently depending on the facts of a particular case. *Id.* at 150 (quoting *Daubert*, 509 U.S. at 593).

"In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Daubert*, 509 U.S. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also D'Tiole v. Sec'y of Health & Hum. Servs.*, No. 15-085V, 2016 WL 7664475, at *24 (Fed. Cl. Spec. Mstr. Nov. 28, 2016) (stating that the Vaccine Act "require[s] a chain of reliable propositions supporting [a] petitioner's theory[]").

Dr. Steinman presented a theory centered on molecular mimicry but revised his theory over time with respect to which proteins in the body were cross reacting with components of FluMist. In his first expert report, he stated that "[t]he nucleoprotein in FluMist [] cross-reacts with hypocretin receptor 2. An immune response to hypocretin receptor is highly likely to underlie the

pathogenesis of narcolepsy [].” Pet’r’s Ex. 14 at 17. In his third expert report, however, Dr. Steinman stated that “[m]olecular mimicry describes how the 2012 FluMist [] vaccine has structures that are cross-reactive with orexin. The nucleoprotein in the 2012 FluMist vaccine cross-reacts with orexin. An immune response to orexin is highly likely to underlie the pathogenesis of narcolepsy.” Pet’r’s Ex. 54 at 17. Dr. Steinman indicated during the hearing that he did not wish to classify these as two distinct theories, but he stated that he would choose the latter theory when I asked him to choose one. Tr. 127:2–4. This selection is consistent with Petitioners’ pre-hearing brief, in which Petitioners referenced Dr. Steinman’s amended theory. Pet’r’s Br. at 14–15. Furthermore, special masters, including myself, have repeatedly rejected theories that, like Dr. Steinman’s original theory, relied on the Ahmed article and epidemiological evidence of a link between other types of flu vaccines and narcolepsy. *See D’Tiole*, 2016 WL 7664475; *Dougherty v. Sec’y of Health & Hum. Servs.*, No. 15-1333V, 2018 WL 3989519; *McCollum v. Sec’y of Health & Hum. Servs.*, No. 14-790V, 2017 WL 5386613 (Fed. Cl. Spec. Mstr. Sept. 15, 2017). Thus, I will focus this analysis on Dr. Steinman’s amended theory.

As a preliminary matter, all three experts in this case opined that narcolepsy is more likely than not an autoimmune condition. Dr. MacGinnitie expressed some reservations but still agreed that narcolepsy is most likely autoimmune. Tr. 199:13–17. Dr. Raizen raised the possibility that the HLA-DQB1*0602 allele may have functions unrelated to the immune system but still maintained that narcolepsy is likely an autoimmune condition. Tr. 170:25–171:4; Tr. 189– 190:2. Furthermore, “[t]he proposition that narcolepsy is an immune-mediated condition is fairly well-established[]” in the Program. *McCollum*, 2017 WL 5386613 at, *16; *see also A.T. v. Sec’y of Health & Hum. Servs.*, No. 16-393V, 2021 WL 6495241, at *21 (Fed. Cl. Spec. Mstr. Dec. 17, 2021); *D’Tiole*, 2016 WL 7664475; *Dougherty*, 2018 WL 3989519, at *43. Thus, I find that narcolepsy is more likely than not an autoimmune condition.

Furthermore, I and other special masters have previously accepted molecular mimicry “as an accepted scientific or medical theory in the context of targeted BLAST searches.” *E.M. v. Sec’y of Health & Hum. Servs.*, No. 14-753V, 2021 WL 3477837, at *38 (Fed. Cl. Spec. Mstr. July 9, 2021). However, “mere invocation of [molecular mimicry] does not carry a petitioner’s burden in a Program case.” *Deshler v. Sec’y of Health & Hum. Servs.*, No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020). Although homology demonstrated by a BLAST search can be supportive of a petitioner’s medical theory, “the finding of sequence homology does not necessarily mean the similarity has significance to the immune system.” *Tullio v. Sec’y of Health & Hum. Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr. Dec. 19, 2019). Indeed, special masters have held “that demonstration of homology alone is not enough to establish a preponderant causation theory.” *Caredio v. Sec’y of Health & Hum. Servs.*, No. 17-79V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021).

In this case, Dr. Steinman identified a homology between a portion of the nucleoprotein in the influenza B strains contained in the 2012 FluMist vaccine and an epitope “identified as being a target of cytotoxic T cells found in the cerebrospinal fluid in patients with Type 1 narcolepsy in [Latorre].” Pet’r’s Ex. 54 at 10. I note that Dr. Steinman appeared to misspeak in claiming the epitope **G**T**E**FK**PR**SA**L** as an epitope noted by Latorre et al. Based on Dr. Steinman’s BLAST search results and the graph in the Latorre article that he refers to, it appears that GTEFKPRSAL is an epitope contained in the nucleoprotein of influenza B while the epitope GAEPAPRPCL was

identified as a target of T cells. *Id.*; Pet'r's Ex. 49 at 5 (identifying "MGRRAGAEPAPRPCLGRRCS" as a target of T cells). However, the BLAST search identified "G_E__PR__L" as areas of overlap. Pet'r's Ex. 54 at 10.

Drs. Steinman and MacGinnitie disagreed on whether this five-out-of-ten match was a significant homology that could induce autoimmune disease. Dr. Steinman relied on the Gautam animal studies that he was involved in to show that a five-out-of-ten match was sufficient to induce autoimmunity. Dr. MacGinnitie, however, rejected this reliance, in part, because of the Gautam researchers' use of CFA. Dr. Steinman explained that adjuvants were used in the Gautam studies because the researchers "wanted to see something that happened with high fidelity" when working with ten to twenty, rather than hundreds of thousands of animals." Tr. 89:25–90:4. He concluded that these studies nevertheless demonstrated the amount of homology necessary to result in disease. *See* Tr. 90:23–25. When I asked Dr. MacGinnitie whether adjuvants increase the likelihood of autoimmunity in terms of vaccines rather than animal studies, Dr. MacGinnitie stated that this is "an active area of research." Tr. 240:22–25. However, he acknowledged that "the stronger an immune response you generate to a specific protein, the more chance that, [] if that protein . . . has homology, that molecular mimicry will occur[]" while also noting that adjuvants themselves "work [] by just stimulating general inflammation[.]" Tr. 241:1–6. Furthermore, Dr. MacGinnitie claimed that "Root-Bernstein says you need adjuvants to see autoimmunity and molecular mimicry in animals[.]" Tr. 225:11–12.

I find Dr. Steinman's argument regarding these papers more persuasive. Dr. Steinman provided a cogent explanation for why the use of adjuvants in the Gautam studies facilitated rather than detracted from their results. I note that Root-Bernstein did not state that adjuvants are required in animal models but instead claimed that "all current animal models based on [molecular mimicry theory] require adjuvants[.]" Pet'r's Ex. 68 at 2. Despite Root-Bernstein's statement regarding animal models, he still treated five-out-of-ten as a significant match when evaluating the role of molecular mimicry in human rheumatic heart disease.

Dr. MacGinnitie relied on the Silvanovich article to show that short matches of eight amino acids or fewer are insignificant. Dr. Steinman argued that Silvanovich et al. identified BLAST searches as superior to sliding window searches. Silvanovich et al. stated that "[b]ioinformatic analyses based on FASTA or BLAST algorithms provide a measure of reliability by providing cut-offs (35% identity over at least 80 amino acids), above which significant IgE cross reactivity may be expected to occur []. In the absence of a ranking, matches with *bona fide* IgE-binding motifs are indistinguishable from false-positive matches in a sliding window search." Pet'r's Ex. 58 at 7. Dr. MacGinnitie relied on the general statement that short matches of fewer than eight amino acids were insignificant but did not indicate whether the homology Dr. Steinman found fit within Silvanovich's guideline, therefore indicating reliability in BLAST searches. *Compare with A.T.*, 2021 WL 6495241, at *15 (Respondent's expert noted that the homologies identified by the petitioner did not meet these criteria and identified an additional article by Silvanovich clarifying the meaning of 'expect values.'). In this case, Respondent filed the Wheeler and Bhagwat tutorial to explain the concept of expect values, but it is unclear how this fits in with the standard identified by Silvanovich for evaluating BLAST searches. Furthermore, while Wheeler and Bhagwat noted that BLAST expect values "in the range of 0.001 to 0.0000001 are commonly used to restrict the alignment shown to those of high quality[,]" they also stated that "the BLAST default of '10' is

designed to ensure that no biologically significant alignment is missed." Resp't's Ex. W at 2. The expect value of 5.3 in this case appears well within the range that could be biologically significant, as identified by Wheeler and Bhagwat. Ultimately, I find Dr. MacGinnitie's use of the Silvanovich article to counter Dr. Steinman's opinion too incomplete to be persuasive.

Dr. MacGinnitie also argued that the homology Dr. Steinman found is insignificant because "of significant homology among all viruses, bacteria, and human protein." Tr. 223:16–22. He noted that he performed a BLAST search on GTEFKPRSAL and found several close matches, including with the zinc-finger protein and with the immunoglobulin gamma-chain and that there were many closer matches between the epitope and other components of the human genome than the match between the epitope and hypocretin. Resp't's Ex. V at 4. Dr. Steinman acknowledged the general existence of "massive amount of mimicry[.]" Tr. 112:9–12. However, he noted that he found only one area of mimicry in the components involved in this case. Tr. 112:12–15. Dr. Steinman rejected the significance of the other homologies Dr. MacGinnitie found because the other substances Dr. MacGinnitie mentioned are not used in vaccines. *See* Tr. 113:6–25. During the hearing, I noted that Dr. Steinman sometimes does not find matches when he performs BLAST searches in other cases in the Program. In this case, he only found one match. The fact that Dr. Steinman only found one match cuts against the notion that there are "massive amounts of mimicry" occurring between the vaccine components and proteins involved in this case.

While Dr. MacGinnitie was focused on the other proteins in the body that GTEFKPRSAL, a foreign protein, could have reacted with, Dr. Steinman appeared to identify GTEFKPRSAL as the protein present in the body that entering substances could react with. Dr. Steinman appeared to confuse a protein in the body with a foreign antigen. While Dr. Steinman's argument is less persuasive due to this confusion, I do not hold it against Dr. Steinman. I note the other homologies Respondent identified, but I do not find that they detract from Petitioner's theory. Respondent's experts have not asserted that zinc-finger protein or other proteins that share homology with GTEFKPRSAL play a role in autoimmune conditions. It has generally been established in the Program that homology alone is insufficient to establish molecular mimicry as a theory pursuant to *Althen* prong one. The same reasoning applies here. The identification of multiple homologies, without more information, does not equate with identification of multiple sites of potential molecular mimicry.

Based on the evidence presented, I find that a five-out-of-ten match, by a preponderance of the evidence, could result in molecular mimicry. The question remains of whether Petitioners have presented preponderant evidence, beyond homology, that the components of orexin and influenza B nucleoprotein can cross-react to cause narcolepsy. I find that Petitioners have provided preponderant evidence that this can occur.

Dr. Steinman stated that, in addition to homology, he relied on the Latorre paper and the IEDB. Tr. 107:22–108:4. Explaining the combined significance of his BLAST search and Latorre, Dr. Steinman explained that his BLAST search corresponded to one place "on the orexin molecule[,]" which was an "epitope that was shown in La[t]orre, and that was in a cell in the spinal fluid of an individual with narcolepsy." Tr. 259:24–260:8. Dr. Steinman averred that this is "about as close as we can get to . . . the actual neurons that are destroyed in the brain." *Id.* Dr. Raizen explained that "the destruction of hypocretin neurons[]" is "a key pathophysiologic pillar of type

1 narcolepsy pathogenesis." Resp't's Ex. C at 6. He, in fact, criticized Dr. Steinman's early expert reports because Dr. Steinman did not "connect" his theory to this pillar. *Id.* Likewise, Dr. MacGinnitie criticized Dr. Steinman's early reports because there was "no evidence [] provided that T-cells specific for the proposed cross-reactive fragment of nucleoprotein exist." Resp't's Ex. A at 7. The Latorre article, however, did find evidence of T cells targeting hypocretin in patients with narcolepsy. Moreover, Dr. MacGinnitie explained that "[t]he arm of the immune system that typically kills cells are T cells, and so the fact that there[is] a T cell response against hypocretin . . . in patients with narcolepsy would be sort of strong evidence for [autoimmunity], and provide the mechanism." Tr. 219:1–5. Furthermore, Dr. Raizen stated that the Latorre article "supports a cellular autoimmune mechanism directed against the hypocretin protein." Resp't's Ex. T at 1. I find it significant that Dr. Steinman was able to find a homology between a component of the FluMist vaccine and a portion of orexin identified as a T cell target in the Latorre article, especially in light of Dr. Raizen's statement and Dr. MacGinnitie's assertion that this is strong evidence providing a mechanism of autoimmunity.

Dr. MacGinnitie raised the possibility that the T cells found by Latorre do not play a causative role in narcolepsy. Latorre et al. did not claim to have enough evidence to support that the T cells they found played a role in narcolepsy pathogenesis. However, they did identify some evidence that at least some of the T cells they found may contribute to the destruction of hypocretin neurons. Latorre et al. identified a patient who had type 2 narcolepsy at the time of testing and was found to have high levels of T cells. Pet'r's Ex. 49 at 5. They noted that this patient's condition progressed to type 1 narcolepsy after testing. *Id.* Latorre et al. indicated that more research was needed but noted that this finding of high numbers of T cells in advance of the patient's progression to type 1 narcolepsy "would be consistent with an autoimmune attack that has not (yet) led to a complete loss of neurons that produce [hypocretin]." *Id.* Furthermore, Dr. MacGinnitie himself acknowledged that the role of T cells is to kill other cells and that Latorre et al.'s finding of T cells targeting hypocretin in narcoleptic patients represents "strong evidence" of autoimmunity and "provide[s] the mechanism." Tr. 219:1–5

Dr. MacGinnitie argued that the Latorre paper did not support molecular mimicry between influenza B and hypocretin because the authors stated that they did not find evidence of cross reactivity between hypocretin and the flu vaccine. When asked, Dr. MacGinnitie did not know whether the flu vaccine Latorre et al. studied contained any nucleoprotein. Tr. 218:15–17. Dr. Steinman stated, however, that he looked into the Influvac vaccine studied by Latorre et al. and found that it did not contain the nucleoprotein. Tr. 103:9–18. Dr. MacGinnitie also noted that Latorre et al. found T cells which were restricted to HLA-DR, rather than HLA-DQ, types. Dr. MacGinnitie stated that it is not clear why this would be but speculated that it may be related to the fact that the researchers "incubated [the T cells] with influenza antigens[] . . . ." Tr. 219:16–21. Dr. MacGinnitie noted that T cells were found in three controls. Resp't's Ex. S at 3. Dr. MacGinnitie nevertheless acknowledged that the discovery of these T cells supported that narcolepsy is autoimmune and provided a mechanism for autoimmunity. Ultimately, I find that Respondent's attempts to rebut Petitioners' contentions based on the Latorre paper were unpersuasive and at times provided support for Petitioners' theory.

While relevant, I find Dr. Steinman's use of the IEDB less persuasive than his use of BLAST searches and the Latorre article. It is notable that the IEDB identified influenza B

nucleoproteins that are a nine-out-of-ten match to the influenza B nucleoprotein found in FluMist, as this indicates that immune responses to similar nucleoproteins have been found. While this adds some support to Petitioners' theory, the IEDB results Dr. Steinman presented do not include enough context to be particularly useful in this case. The results do not indicate how and in whom immune responses to the nucleoproteins were detected. *See* Pet'r's Ex. 65 at 11. They do not relate these responses to narcolepsy or any other autoimmune condition. *See id.* Nevertheless, the other evidence Petitioners and Dr. Steinman have presented is persuasive.

In previous narcolepsy cases in the Program, special masters have carefully evaluated epidemiological evidence presented by the parties. As a general matter, Program petitioners are not required to present epidemiologic evidence to satisfy their causation burden under *Althen*. *Moberly*, 592 F.3d at 1325. However, there is no requirement that special masters "ignore probative epidemiological evidence that undermines [a] petitioner's theory." *D'Tiole v. Sec'y of Health & Hum. Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018) (determining that Special Master Corcoran's reliance on the Duffy study "did not improperly raise the standard in *Althen* beyond a preponderance of the evidence"); *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury."); *Godfrey v. Sec'y of Health & Hum. Servs.*, No. 10-565V, 2014 WL 3058353, at *19 (Fed. Cl. Spec. Mstr. June 11, 2014) ("This is not a case where epidemiologic evidence is lacking. The epidemiology exists, and is not supportive of the theory."). However, negative epidemiological studies are not necessarily fatal to a petitioner's claim. *See Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1149 (holding that a special master's decision was not arbitrary or capricious when he "relied on a preponderance of relevant scientific and medical evidence" about the particular vaccine rather than epidemiological studies related to general DPT vaccines); *D'Tiole*, 2016 WL 7664475, at *22 ("Indeed, because vaccine injuries are rare events, the fact that a particular epidemiologic study suggests a vaccine is generally safe should not prevent a claimant from prevailing (assuming the other *Althen* factors are met)."); *Harris v. Sec'y of Health & Hum. Servs.*, No. 10-322V, 2014 WL 3159377, at *11 (Fed. Cl. Spec. Mstr. June 10, 2014) ("Epidemiological studies cannot prove a negative. It is always possible that another epidemiological study involving a bigger population will detect an increased risk not otherwise apparent in smaller studies.").

Like in other narcolepsy cases, Petitioners have presented some evidence that adjuvanted H1N1 flu vaccines, such as Pandemrix, were associated with higher narcolepsy rates. *See* Pet'r's Ex. 12, ECF No. 6-2;[61] Pet'r's Ex. 33; Pet'r's Ex. 61. In *D'Tiole*, a case which also centered on FluMist, Special Master Corcoran rejected the petitioner's use of an association between Pandemrix and narcolepsy. He noted that the petitioner "propose[d] that because Pandemrix has been credibly associated with narcolepsy, it is equally plausible that the FluMist formulation—an LAIV—of the vaccine would do the same, merely because it also contains the H1N1 wild virus strain." *D'Tiole*, 2016 WL 7664475, at *20. He explained that the Ahmed articles, also filed in this case, "stand for the proposition that something about the process of inactivating the viral strain in manufacturing that form of the flu vaccine is associated with increasing the number of nucleotide

[61] Yves Dauvilliers et al., *Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France*, 136 BRAIN 2486 (2013).

antibodies—not that the mere presence of H1N1 proteins in any form, and in any version of the flu vaccine, will inevitably result in sufficient levels of the antibodies to produce the same cross-reactive autoimmune process." *Id.* at *21. He noted that FluMist is "subject to a wholly different manufacturing process[]" and that the petitioner had "not shown why, or how, the LAIV version would be comparable to Pandemrix" or other adjuvanted pandemic vaccines "in increasing the nucleoprotein antibodies." *Id.* Special Master Corcoran used similar reasoning in *McCollum*. *See McCollum*, 2017 WL 5386613, at *16 (concluding that the petitioner had not shown that "science regarding a *different* form of flu vaccine [can] be applied to the version [the petitioner] allegedly received[]") (emphasis in original). In *Dougherty*, I reasoned that Pandemrix and Fluzone, the vaccine at issue in that case, were "not analogous[] because they differ in manufacturing, viral strains, and the presence of an adjuvant." *Dougherty*, 2018 WL 3989519, at *42.

The epidemiological studies exploring links between adjuvanted H1N1 vaccines and narcolepsy are less relevant to Petitioners' theory than theories in previous cases because Petitioners' theory is focused on influenza B strains. H1N1 is an influenza A strain. Dr. Steinman averred that the nucleoproteins between influenza A and B "are not dissimilar" and "still are nucleoproteins [in the flu] vaccine." Tr. 123:18–22. Yet, Dr. Steinman presented homology between influenza B nucleoprotein and an area of hypocretin identified in the Latorre article and not a homology involving influenza A. This implies that influenza A and B nucleoproteins are somewhat dissimilar, at least in terms of Petitioners' theory involving molecular mimicry. Petitioners have not presented evidence that an influenza A nucleoprotein, or an H1N1 nucleoprotein, shares homology with a region of orexin identified by Latorre et al. In light of Petitioners' focus on influenza B and the persuasive reasoning in previous narcolepsy cases, I find that the medical literature in this case linking H1N1 vaccines or infection to narcolepsy does not aid Petitioners in satisfying their burden.

As in previous cases, the sole epidemiological evidence that pertains specifically to the type of vaccine V.H. received is the Duffy study. Although Dr. Steinman is highly critical of the Duffy study, special masters have previously found it to be persuasive evidence against petitioners' theories. However, Special Master Corcoran noted that "the Duffy epidemiologic study stood as very strong evidence rebutting an association between an *LAIV containing the H1N1 strain* and narcolepsy." *D'Tiole*, 2016 WL 7664475, at *22 (emphasis added). In this case, I will focus primarily on whether the Duffy study rebuts an association between LAIVs containing influenza B and narcolepsy.

Duffy et al. followed 650,995 people who received flu vaccines during the 2009 pandemic and 870,530 people who received flu vaccines during the 2010–2011 flu season. Resp't's Ex. A, Tab 17 at 1. The researchers followed recipients of four different types of vaccines. *Id.* at 5. Of the four groups, the group that received LAIVs containing influenza B strains was the smallest. *See id.* For the 2009 pandemic, the researchers followed 439,031 people who received MIVs vaccines and 211,964 people who received MLAIVs. *Id.* For the 2010–2011 flu season, the researchers followed 740,982 people who received TIVs and 129,548 who received LAIVs. *Id.* The researchers found only two cases of narcolepsy within 180 days post vaccination. *Id.* These were in ten to nineteen-year-olds who received TIVs. *Id.* Because the monovalent vaccines, including the MLAIV, did not contain influenza B strains, the findings pertaining to those vaccines hold less direct relevance to Petitioners' theory. Of the 870,530 individuals who were followed after

receiving 2010–2011 seasonal vaccines, 740,982 received a different type of vaccine than the one V.H. received. Thus, if evaluated specifically in terms of results for LAIVs containing influenza B, the sample size, while still large, is smaller than initially indicated. This is significant because "[a] study with a greater sample size, and therefore sufficient statistical power, can more persuasively support a determination as to whether a causal link exists." *D'Tiole*, 2016 WL 7664475, at *22 (citing Michael D. Green et al., *Reference Guide on Epidemiology*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 549, 582 (Fed. Judicial Center, 3d ed. 2011 ("Green")).

Of the 129,548 people between ages ten and twenty-nine who received LAIVs, 81,410 were under the age of ten. Resp't's Ex. A, Tab 17 at 5. Notably, this age group had the lowest expected incidence rate of the three age groups studied. For people under age ten, the expected incidence rate was 1.01/100,000, while the expected incidence rates for ten to nineteen-year-olds and twenty to twenty-nine-year-olds were 3.84/100,000 and 1.84/100,000, respectively. *Id.* The expected number of cases based on the total number of recipients of LAIVs was 1.26, and the expected number of cases for recipients of LAIVs under age ten was 0.4. *Id.* "[T]he predictive strength of an incidence rate is directly tied to the 'power' of an epidemiologic study, which is in turn dependent on the sample size." *D'Tiole*, 2016 WL 7664475, at *22 (citing Green at 576, 582). Furthermore, Dr. Steinman criticized the expected incidence rate in the Duffy study because of the "relative paucity of [HLA-DQB1*0602] patients in the" United States. Pet'r's Ex. 43 at 10. This "relative paucity" may be significant when viewed in terms of the smaller number of patients who received LAIVs containing influenza B and the lower expected incidence rate for children under age ten.

I award the Duffy study some weight in this case, but I do not find that it is as persuasive in rebutting Petitioners' theory as it has been found in previous Program narcolepsy cases. It is significant that Duffy et al. studied multiple formulations of flu vaccines, found no increased risk of narcolepsy within 180 days post vaccination, and found no cases of narcolepsy within 180 days of LAIV vaccination. It is further notable that the researchers found no increased risk related to the 2010–2011 LAIV in all three age groups studied, including V.H.'s age group. However, because of the relatively low expected incidence rate for children under ten and the fact that recipients of LAIVs containing influenza B was the smallest of the four groups studied, I find the study's power more limited in this case. In particular, the relative rarity of narcolepsy in children in V.H.'s age group increases the likelihood that an even bigger sample size may have been necessary to observe an increased risk of narcolepsy in young children who received seasonal FluMist vaccines. Although I have considered the Duffy study and awarded it some weight, I must evaluate it along with the rest of the evidence in the record supporting Petitioners' theory.

Petitioners have presented evidence of a homology between a portion of the FluMist vaccine and a portion of hypocretin targeted by T cells in a small study of narcolepsy patients. They have presented evidence that this homology is sufficient to induce autoimmunity, and the epidemiological evidence neither significantly adds to nor detracts from Petitioners' theory. However, there are still some potential problems with Petitioners' theory. The experts have indicated that the discovery of T cells in narcolepsy patients is a recent one, and both parties' experts have made clear that they would like to see further research into the role of the T cells in narcolepsy pathogenesis. Dr. Steinman explained why observing direct evidence of an autoimmune process would have been infeasible in narcolepsy patients generally and in this case

specifically. Addressing the notion that narcolepsy is not associated with neuroinflammation, Dr. Steinman explained that brains, unlike other body parts, are not readily biopsied. Tr. 135:2–8. He noted that closer examination of the brain in narcoleptic patients could show "the criminal immune system attacking itself." Tr. 135:9–16. However, "these are inaccessible[,] and it may be [a] hit and run. They may hit it and the neurons are gone and then you do[not] get to see them." Tr. 135:10–14. Dr. Raizen echoed Dr. Steinman's point about accessing the brain, explaining that it would not be "entirely fair[]" to apply knowledge on other autoimmune diseases to narcolepsy "because of the difficulty in assessing the part of the brain that needs to be assessed." Tr. 173:4–12. He stated that inflammation has not been found in narcolepsy patients and explained that MRIs, "while very powerful and used to assess inflammation for certain neurological diseases, may not be sensitive enough to pick up inflammation in the small part of the brain called the hypothalamus." Tr. 180:15–20. He continued that researchers' failure to discover inflammation during autopsies of brains of narcoleptic patients did not mean that inflammation was not present earlier. Tr. 180:24–181:2. Dr. Raizen also noted that narcolepsy is not associated with a prodrome and that "there[is] often a long lag between symptom onset and diagnosis[] . . . ." Tr. 170:10–16. Unlike in previous cases, Petitioners' theory centers on hypocretin rather than its receptors, which are more widespread in the body. As Dr. Raizen explained, hypocretin comes from the preprohypocretin protein, which is "found only in the small number of neurons deep in the brain in . . . [the] posterior lateral hypothalamus." Resp't's Ex. C at 4. Dr. Steinman opined that it may have been possible to observe an autoimmune process in this case. He stated that "had we done all the sophisticated tests that we[are] capable of running[] . . . and did a Latorre type of investigation, we might have found [evidence of autoimmunity], but it all depends on what we were looking for or whether there was a search for it." Tr. 114:21–115:1. Dr. Steinman added, however, that "[t]hese are not common tests or research tests." *Id.* Dr. Steinman asserted that "we might be running Latorre type tests on narcoleptic patients in the not-too-distant future." Tr. 115:8–12.

Although the experts have indicated research into the mechanisms involved in narcolepsy pathogenesis is incomplete and have explained the difficulties involved in pursuing at least some avenues of further research, I do not hold this against Petitioners. Indeed, "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280 (holding that a petitioner was entitled to compensation although her theory involved "a sequence hitherto unproven in medicine[]"). Special masters may not treat "a paucity of medical literature supporting a particular theory of causation . . . as a bar to recovery." *Andreu*, 569 F.3d at 1367. Because this is a "field bereft of complete and direct proof[,] . . . most expert opinions extrapolate from existing data and knowledge." *Daily v. Sec'y of Health & Hum. Servs.*, No. 07-173V, 2011 WL 2174535, at *6 (Fed. Cl. Spec. Mstr. May 11, 2011); *see also Paluck v. Sec'y of Health & Hum. Servs.*, 104 Fed. Cl. 457, 474 (2012) ("The fact that the research investigating a link between vaccinations and oxidative stress is of quite recent origin is not fatal to the theory. Inquiry into the subject is just beginning, as the very recent dates of the articles show.").

Further research to expand on the Latorre article would be helpful, but that does not preclude Petitioners from satisfying *Althen* prong one by a preponderant standard. The nature of the injury and mechanism at issue in this case presents some difficulties for some avenues of further research. However, as Dr. Steinman indicated, future Latorre-style tests may provide further insight into narcolepsy pathogenesis, including its relationship to the FluMist vaccine.

Petitioners have not presented direct evidence linking the FluMist vaccine to narcolepsy or direct evidence that their proposed mechanism occurs, but neither is required to satisfy prong one. I find that Petitioners have presented a chain of reliable evidence resulting in an overall sound and reliable theory. The experts have presented evidence that T cells targeting hypocretin neurons likely play an important role in narcolepsy pathogenesis. Dr. Steinman showed that T cells targeting an area in hypocretin are present in narcolepsy patients. He demonstrated a preponderantly significant homology between that area and the nucleoprotein of the influenza B strain contained in the FluMist vaccine that V.H. received. Thus, I conclude that Petitioners have, by a preponderant standard, presented a legally probable theory based on a sound and reliable explanation in this case.

B. *Althen* Prong Two

Under the second prong of *Althen*, a petitioner must prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; instead, the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original). The special master in *Pafford* noted petitioners "must prove [] both that her vaccinations were a substantial factor in causing the illness . . . and that the harm would not have occurred in the absence of the vaccination." 2004 WL 1717359, at *4 (citing *Shyface*, 165 F.3d at 1352). A reputable medical or scientific explanation must support this logical sequence of cause and effect. *Hodges v. Sec'y of Health & Hum. Servs.*, 9 F.3d 958, 961 (Fed Cir. 1993) (citation omitted). Nevertheless, "[r]equiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." *Capizzano*, 440 F.3d at 1325–26. "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

In Program cases, contemporaneous medical records and the opinions of treating physicians are favored. *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). Indeed, when reviewing the record, a special master must consider the opinions of treating physicians. *Capizzano*, 440 F.3d at 1326. This is because "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Id.* In addition, "[m]edical records, in general, warrant consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events." *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). While a special master must consider these opinions and records, they are not "binding on the special master or court." 42 U.S.C. § 300aa-13(b)(1). Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ." *Id.*

In previous narcolepsy cases, I and other special masters have determined that petitioners failed to satisfy prong two when they were unable to present evidence demonstrating that they experienced autoimmunity leading up to their development of narcolepsy. *D'Tiole,* 2016 WL 7664475, at *24 ("The record lacks direct or indirect evidence of the existence of an autoimmune post-vaccination reaction, reflected by some other test result or symptom."); *Dougherty*, 2018 WL 3989519, at *47 ("There is no evidence that supports an autoimmune reaction in [the p]etitioner's case."). Likewise, in this case, Dr. Steinman acknowledged that there is "nothing in the medical record" indicating that V.H. experienced an autoimmune process.

Program petitioners may be able to prevail on prong two even when medical records do not contain direct evidence that the biological mechanism alleged actually occurred and caused injury. *See*, *E.M.*, 2021 WL 3477837, at *40–42 (finding that a petitioner satisfied prong two when she was on a medication that prevented accurate antibody testing but when a majority of her treating physicians opined that her condition was caused by her vaccination and when the petitioner's medical theory was consistent with the facts of the case). In this case, Petitioners were able to explain why obtaining evidence of an autoimmune process through examination of V.H.'s brain would be infeasible. However, I find that Petitioners did not present other evidence sufficient to satisfy their burden under prong two.

It is well established in the Program that temporal proximity between a vaccination and injury is insufficient to support causation. *See*, *e.g.*, *D'Tiole*, 2016 WL 7664475, at *24 ("Dr. Steinman largely appears to assume that the fact that narcolepsy follow[ing] vaccination is proof enough of a relationship—an assumption the Program soundly rejects."); *Moberly*, 592 F.3d at 1323 (quoting *Althen*, 418 F.3d at 1278) ("[N]either a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation."); *Sumner v. Sec'y of Health & Hum. Servs.*, No. 99-946V, 2015 WL 5173644, at *9 (Fed. Cl. Spec. Mstr. Aug. 13, 2015) ("[W]here a petitioner's expert views the temporal relationship as the 'key' indicator of causation, the claim must fail."). In this case, as in *D'Tiole*, Dr. Steinman's conclusion that V.H.'s flu vaccination actually caused his narcolepsy is based on temporal proximity. Dr. Steinman opined that V.H. likely had a recall response following his September 24, 2012 FluMist vaccination since "he had FluMist before, and that fits with what we know about recall responses." Tr. 116:4–6. When I asked Dr. Steinman to explain how he could argue that V.H. experienced a recall response when there was no evidence that he experienced an acute immune response to his first FluMist vaccination, Dr. Steinman explained that the evidence that V.H. experienced a recall response was that the September 24, 2012 FluMist vaccination "was [V.H.'s] second shot and it took a few weeks to a month or so to have the . . . manifestations apparent in narcolepsy." Tr. 144:5–10. Dr. Steinman explained that "a second vaccine, by definition, triggers a recall response[]" and that a recall response is almost always present if a patient suffers a vaccine injury after receiving a vaccine more than once. Tr. 146:10–16. However, Dr. Steinman conceded that he had no evidence that a recall response occurred in this case besides the manifestation of V.H.'s narcolepsy. Tr. 146:3–6. Indeed, he began with his conclusion to prove the mechanism. Dr. Steinman's assertion that V.H. experienced a recall response that caused his narcolepsy is based on temporal proximity alone. This abductive reasoning that the vaccine must be the cause is not sufficient to meet the standard because, to establish causation, more is needed than a chronological relationship. While Petitioners are not required to present direct evidence of recall/rechallenge, Dr.

Steinman has identified recall as the type of immune response that triggered V.H.'s autoimmunity. Dr. Steinman cannot simply state V.H.'s injury is presumed evidence of the recall, the recall is presumed evidence of the autoimmunity, and the autoimmunity is presumed evidence of vaccine causation, without some support that these processes actually occurred in V.H.'s case. Dr. Steinman's conclusions are, by his own concession, speculation based solely on chronology. Tr. 146:3–6. Alternatively, Dr. MacGinnitie disagreed that V.H. experienced a recall response. Tr. 251:21–23. He noted that the strains contained in flu vaccines are adjusted yearly and that this is why people receive yearly flu vaccinations. Tr. 251:23–25. The Wrammert et al. article, however, contradicts Dr. MacGinnitie's assertion on the purpose of recurring flu vaccinations. *See* Pet'r's Ex. 41 at 1 ("[A]nnual vaccinations are given to maintain protective levels of antibody against the currently circulating strains."). Neither expert has provided evidence to determine whether a recall has occurred, but it is the Petitioners' burden to establish any alleged fact beyond a mere temporal relationship. Petitioners have presented insufficient evidence that V.H. experienced such a sequence of events.

V.H.'s medical records indicate that V.H.'s physicians considered the FluMist vaccine as a potential cause of his condition because of temporal association and because of research on links between vaccines and narcolepsy. However, his medical records also indicate that his providers stopped short of opining that V.H.'s flu vaccination was the cause, or the likely cause, of his narcolepsy. I must emphasize that evidence of a treater's belief that an injury is vaccine-caused is not required, but it can be helpful in supporting causation. Indeed, treating physicians' opinions on causation are awarded significant weight in the Program. However, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *A.T.*, 2021 WL 6495241, at *27 (quoting *Isaac v. Sec'y of Health & Hum. Servs.*, No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012)). Furthermore, a treating physician's "statements of mere suspicion fall short of an opinion supporting a vaccine-related" injury. *Id.* A special master may find evidence from treating physicians unpersuasive when they "considered, though did not conclude, that" a petitioner's vaccination caused her condition. *Id.* (citing *Cedillo*, 617 F.3d at 1348 (determining that a special master's decision to attribute little weight to the opinions of treating physicians was not arbitrary or capricious when "none of the treating physicians concluded that the MMR vaccine caused [the petitioner's] autism[]")). The treating physician's opinions merit discussion in this case because of the notes in V.H.'s medical records.

When V.H. presented to Dr. Pfeffer for a sleep study on March 27, 2013, Dr. Pfeffer noted that V.H.'s symptoms began following his September 24, 2012 flu vaccination and that she "raise[d] this history given the potential for acquired narcolepsy related to H1N1 vaccine seen more commonly at younger ages." Pet'r's Ex. 3 at 15. On March 28, 2013, Dr. Pfeffer stated that it was "[q]uite concerning[]" that V.H. received a flu vaccine in September of 2012 and began experiencing excessive daytime sleepiness in October or November of the same year. Pet'r's Ex. 3 at 1. She wrote that "[v]accine-related narcolepsy is becoming an increasing concern, involving all vaccines, but most commonly flu[.]" *Id.* Dr. Pfeffer noted that she was addressing "the relationship between the flu vaccine, his sleepiness, and his increase in appetite in light of concerns that he may have acquired an H1N1 vaccine related insult to his hypothalamus, specifically affecting his satiety center, but more concerningly affecting the sleep/wake center, within which are the orexin secreting cells." *Id.* Despite these concerns, Dr. Pfeffer initially diagnosed V.H. with *idiopathic* hypersomnia that could evolve into narcolepsy following his April 13, 2013 MSLT. *Id.*

at 39. On July 21, 2014, when V.H. returned to Dr. Pfeffer, she noted that V.H. had been diagnosed with narcolepsy with cataplexy, which "*may or may not* have been related to a flu vaccine." Pet'r's Ex. 3 at 75 (emphasis added). Furthermore, it appears that Dr. Pfeffer's consideration of a possible link centered on the H1N1 component of the FluMist vaccine, which is not the component involved in Petitioners' proposed theory. Thus, her statements do not help establish whether Petitioners' proposed biological mechanism actually occurred in this case.

When V.H. presented to Dr. Arora and Dr. Mignot on September 18, 2013, Dr. Arora and Mignot's assessment was "narcolepsy with cataplexy *after* Flumyst [sic] vaccine[]" after Petitioners reported that V.H.'s symptoms began four to six weeks post vaccination. Pet'r's Ex. 5 at 7 (emphasis added). This note goes to chronology rather than causation. After consideration of the entire medical record, I do not find that the notations from V.H.'s treating physicians add persuasive support for causation.

I conclude that Petitioners have not provided preponderant evidence that V.H. suffered an autoimmune reaction following his vaccination, or that V.H.'s September 24, 2012 flu vaccination caused his narcolepsy with cataplexy.

C. *Althen* Prong Three

To satisfy the third *Althen* prong, a petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352. Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Hum. Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Hum. Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Grant*, 956 F.2d at 1148 ("[T]he inoculation is not the cause of every event that occurs within the ten[-]day period . . . [w]ithout more, this proximate temporal relationship will not support a finding of causation." (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

I find that Petitioners have provided preponderant evidence that V.H.'s narcolepsy manifested between late October of 2012 and November of 2012. There was some suggestion in V.H.'s medical records that his sleep disturbance may have predated his September 24, 2012 vaccination. Ms. Henkel, however, credibly explained that V.H.'s previous sleep issue was in regard to a change in his nap schedule and resolved prior to his September 24, 2012 vaccination.

See Tr. 16–17. Petitioners at times in the medical records provided slightly different accounts of onset. But Ms. Henkel explained that she may have at times misestimated how long it had been since V.H.'s sleep disturbance began and may have been referring to when V.H.'s symptoms had progressively worsened. *See* Tr. 45–46. Ms. Henkel did not report that V.H. was experiencing sleep problems during his medical visit for abdominal pain in November of 2012. Tr. 21:12–20. However, she testified that V.H.'s abdominal pain accompanied sleep disturbance but that she did not yet realize that his sleep disturbance may be unrelated to abdominal pain or a growth spurt. *Id.* She also explained that she remembered V.H. experiencing sleep problems in October and November because she had a newborn baby at the time who was also sleeping during the day. Tr. 19:9–18. I find Ms. Henkel's explanations and the contextual information she provided credible and probative of the onset of V.H.'s condition.

Dr. Steinman has opined that this onset, approximately four to six weeks post vaccination, is appropriate for a recall response. He also presented evidence that narcolepsy associated with Pandemrix occurred approximately two months post vaccination and that narcolepsy that was possibly associated with H1N1 infection occurred approximately six months post infection, in the Ahmed and Han articles, respectively. *See* Pet'r's Ex. 15 at 3; Pet'r's Ex. 64 at 1. Dr. Steinman is an expert in immunology, and his opinions regarding recall responses have been accepted in the Program before. Despite Dr. Steinman's expertise, it is unclear how an LAIV, which mimics an infection according to Petitioners' own medical literature, would trigger a recall response within the same timeframe as an inactivated vaccine. *See* Pet'r's Ex. 15 at 5 ("Due to their similarity in structure with the natural virus or bacteria, live vaccines could induce molecular mimicry similar to that associated with the natural infection []."") Ahmed et al., citing the Han study, claimed that narcolepsy following infection with H1N1 occurred six months post vaccination, but that is not the timeframe proposed by Petitioners as appropriate in this case. While neither Ahmed et al. nor Han et al. appeared to consider recall responses in their discussion, Dr. Steinman has not explained how a recall response would impact the timing of disease onset following either an LAIV or an infection. I find that Petitioners have provided insufficient evidence in this case of what an appropriate timeframe between V.H.'s second FluMist vaccination and narcolepsy onset would be. Thus, I find that Petitioners have not provided preponderant evidence of a proximate temporal relationship between V.H.'s vaccination and narcolepsy onset.

VI. Conclusion

After a careful review of the record, Petitioners have failed to prove by preponderant evidence that V.H.'s narcolepsy was caused-in-fact by his September 24, 2012 flu vaccination. Accordingly, I have no choice but to **DENY** Petitioners' claim and **DISMISS** their petition.[62]

IT IS SO ORDERED.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master

[62] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.